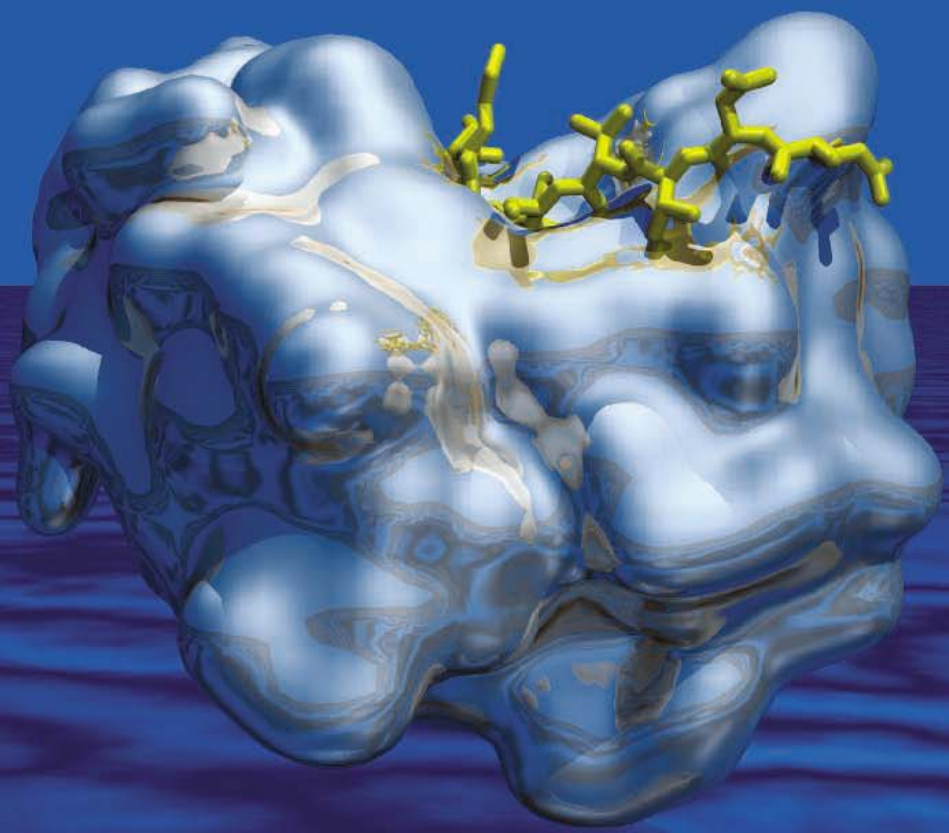
3 February 2006 | $10

Science



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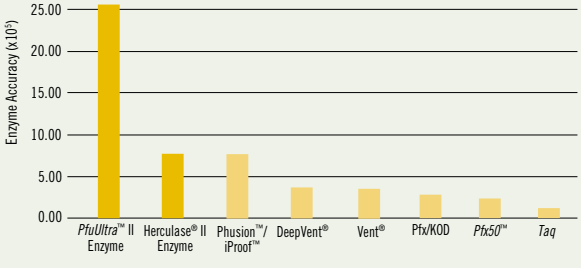

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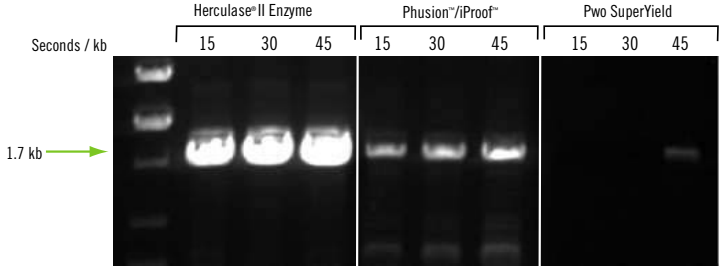

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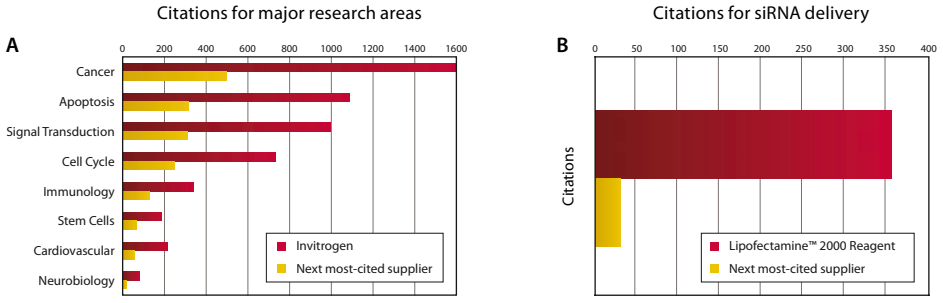
Figure 1—Most widely cited transfection reagents



Invitrogen transfection reagents are the most cited in the scientific literature compared to all other suppliers. A. Citation results from the top two transfection reagent companies from January-June 2005 in major research fields. B. For siRNA delivery, Lipofectamine™ 2000 Reagent is cited over ten times more often than the next-cited reagent on the market. Data obtained through www.highwire.org.

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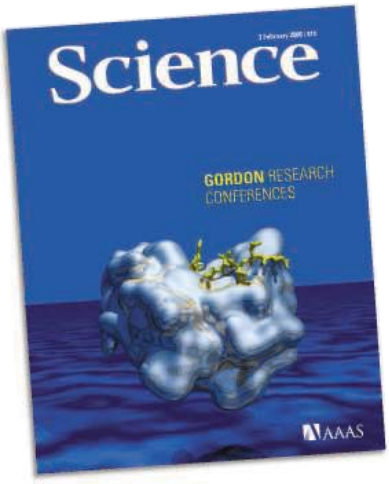
Volume 311, Issue 5761



COVER

The structure of the hepatitis C virus NS5A-5B natural substrate (yellow), bound to the active site of the NS3-4A protease (blue), has formed the basis for designing novel protease inhibitors that directly interfere with replication of this virus. This image shows the shallow, solvent-exposed binding groove of the NS3-4A enzyme. The Gordon Research Conference on Medicinal Chemistry will be held from 6 to 11 August 2006 at Colby Sawyer College, New London, NH. The schedules for the 2006 Gordon Research Conferences begin on page 676.

Image: James Griffith

DEPARTMENTS

EDITORIAL

NEWS OF THE WEEK

NEWS FOCUS

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POLICY FORUM

PERSPECTIVES

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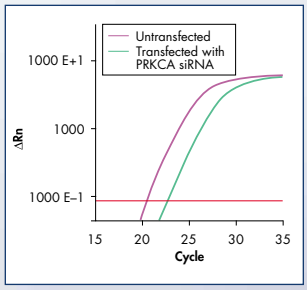
Systems Biology — RNAi and Gene Expression Analysis

GeneGlobe — the world's largest database of matching siRNAs and RT-PCR assays

New



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Science

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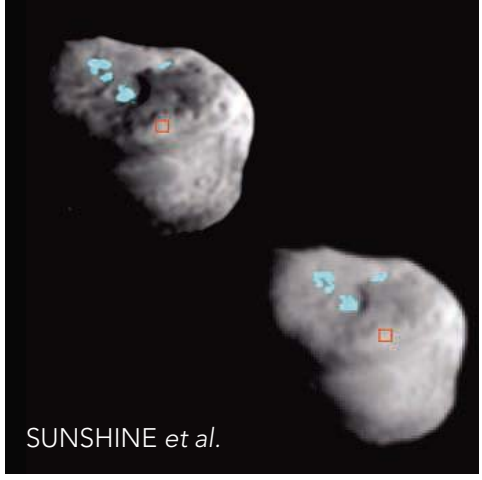
EPIDEMIOLOGY

The Global Impact of Scaling-Up HIV/AIDS Prevention Programs in Low- and Middle-Income Countries
J. Stover et al.
Implementation of AIDS prevention measures targeting sexual transmission and drug users could prevent 30 million new infections in the next 10 years.
>> Perspective p. 620; Report p. 664
10.1126/science.1121176

MEDICINE

BREVIA: Cellular Senescence in Aging Primates
U. Herbig, M. Ferreira, L. Condel, D. Carey, J. M. Sedivy
As baboons age, cells that have become irreversibly senescent accumulate in various tissues, likely contributing to the aging of the whole animal.
10.1126/science.1122446

Late Precambrian Oxygenation; Inception of the Clay Mineral Factory
M. Kennedy, M. Droser, L. M. Mayer, D. Pevear, D. Mrofka
The development of an oxygen-rich atmosphere during the Neoproterozoic was the result of an increase in the rate of clay deposition caused by the spread of terrestrial vegetation.
10.1126/science.1118929

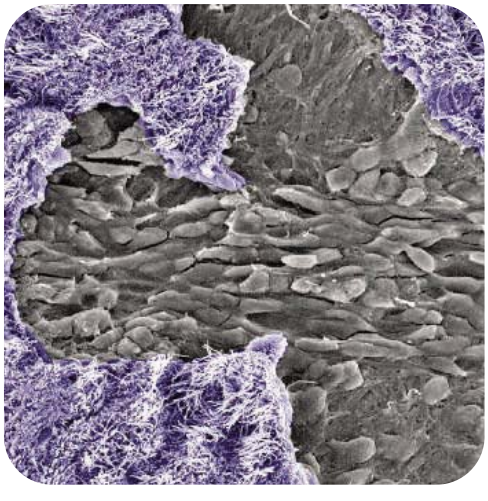


MOSFET-Embedded Microcantilevers for Measuring Deflection in Biomolecular Sensors
G. Shekhawat, S.-H. Tark, V. P. Dravid
The small bending created when biomolecules bind to receptors on a microfabricated cantilever can be detected with an embedded transistor, forming a microsensor.
10.1126/science.1122588

Exposed Water Ice Deposits on the Surface of Comet Tempel 1
J. M. Sunshine et al.
Deep Impact has found three patches of water ice on comet Tempel 1, but these are insufficient to account for the water output observed in outgassing, implying a subsurface source.
10.1126/science.1123632

TECHNICAL COMMENT ABSTRACT

REVIEW



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RESEARCH ARTICLE

REPORTS

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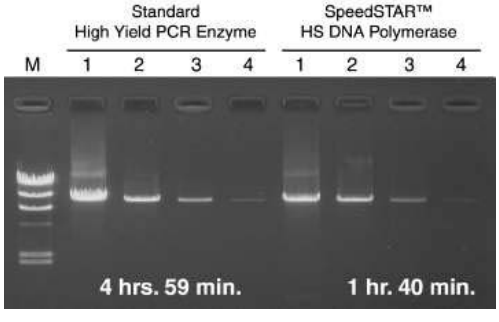

Amplification of an 8.5 kb Human Genomic DNA Fragment using a Standard High Yield Polymerase and SpeedSTAR™.

Fragment size	Target genome	Regular PCR	SpeedSTAR™ HS Polymerase
1 kb-2 kb	*E. coli*	96 min (2-step)	33 min
4 kb- 6 kb	*E. coli*	226 min (2-step)	53 min
8 kb- 10 kb	*E. coli*	346 min (2-step)	83 min
18 kb-20 kb	*E. coli*	8 hrs 16 min (2-step)	3 hrs 29 min
Genomic 8.5 kb	Human	4 hrs 59 min (2-step)	1 hr 40 min
Genomic 17.5 kb	Human	8 hrs 16 min (2-step)	3 hr 29 min

Comparison of SpeedSTAR™ and Standard PCR Enzyme Reaction Times on Fragments of Varying Sizes.

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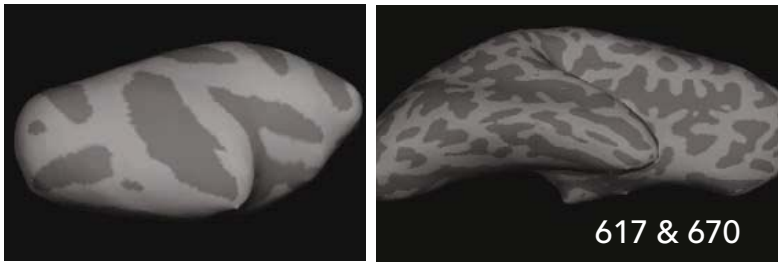

REPORTS *CONTINUED...*

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CONTENTS continued **>>**

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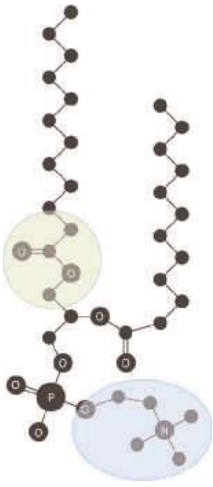

Membrane phospholipid diversity.

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EDITORIAL GUIDE: Focus Issue—Signaling Lipids
N. R. Gough
Lipids play diverse roles in cell signaling.

PERSPECTIVE: Role of Docosahexaenoic Acid in Neuronal Plasma Membranes
J. A. Glomset
Small differences in the structures of membrane phosphoglycerides may have major implications for cell signaling.

PERSPECTIVE: Building Signaling Complexes at the Membrane
W. Cho
Multiple interactions promote the formation of specific signaling complexes at cellular membranes.

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Prions Present a Positive Side
The "mad cow" proteins also help blood stem cells survive.

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Darkness and extreme heat are no problem for algae converting nitrogen to nutrients.

You've Got *What* in Your Ears?
A small genetic change determines whether your earwax is wet or dry.

Bridging the independence gap.

SCIENCE **CAREERS**

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US: A Bridge to Independence
B. Benderly
Despite a tight budget, NIH is moving forward with a plan to boost (some) postdocs' transitions to scientific independence.
>> News story p. 593

UK: Technology Transfer Training
R. Phillips
Next Wave examines training opportunities in the UK for technology transfer professionals.

SPAIN: Getting your Foreign Diploma Recognized in Spain
E. Pain
What impact is a recent Spanish law about recognizing foreign degrees having on young scientists?

GRANTSNET: February 2006 Funding News
J. Fernandez
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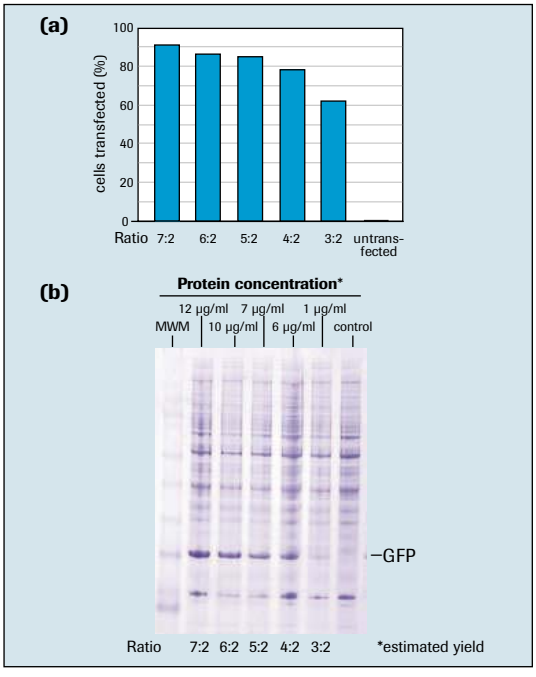

Figure 1: GFP expression in HEK-293 EBNA cells. HEK-293 EBNA suspension-adapted cells were transfected with plasmid DNA for GFP following the recommended protocol, using ratios of 7:2, 6:2, 5:2, 4:2, and 3:2 (µl FuGENE® HD Transfection Reagent:µg plasmid DNA). The percentage of cells transfected (a) was determined 28 hours post transfection and quantity of GFP protein (b) was estimated from the Coomassie Blue-stained gel at 72 hours post transfection.

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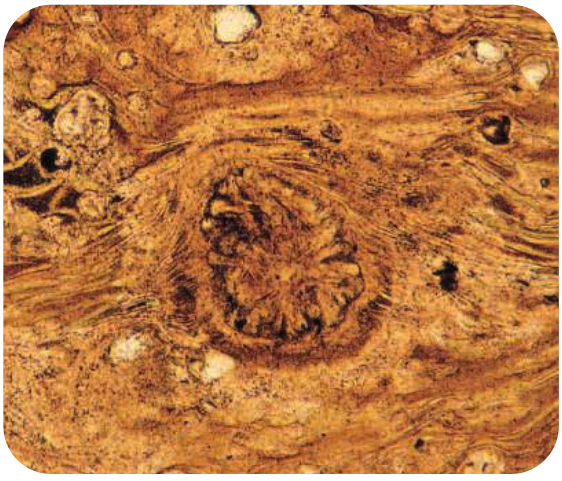


<< Slippery Melt Strands

Some exhumed faults contain small pockets of melted rocks, presumably produced by frictional heat during an earthquake. The role of these melt strands—whether they inhibit faulting or lubricate it—and how they are produced in weak faults has been controversial. **Di Toro *et al.*** (p. 647) have now produced analogous features in the laboratory that they compare with actual field samples from an exposed fault. They used a rotary shear apparatus to slide rocks against each other at conditions that approximate natural earthquakes. Melt pockets were produced that lowered the friction and lubricated rather than sealed the fault.

Assessing Nanomaterial Safety

Scenarios of the dangers of nanotechnology that involve nanorobots running amok in our bodies or the world being taken over by "gray goo" are considered highly unlikely by many experts. However, a great deal remains unknown about the biological effects of human and environmental exposure to nanomaterials. **Nel *et al.*** (p. 622) review the important chemical and biological properties of nanomaterials and outline ways in which the safety and toxicity of these substances can be evaluated.

Magnetic Maps

Magnetic fields on stars like the Sun affect their interiors and their surrounding environment. In strongly convecting stars, turbulence is expected to break up aligned magnetic fields. **Donati *et al.*** (p. 633; see the Perspective by **Basri**) show that in a very-low-mass, fully-convective star, substantial fields remain, including a strong dipole component. The pattern of magnetic fields on the star's surface was recreated from observations of the fine Zeeman splitting of spectral lines caused by magnetic fields and other signatures in polarized light.

Spectroscopy of Coupled Quantum Dots

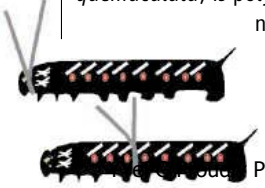
Single and coupled multiple quantum-dot structures have long been proposed as systems for storing and manipulating information in quantum information processing. However, finding routes to get the coupled dots to communicate are only now being explored. **Stinaff *et al.*** (p. 636, published online 12 January) present a spectroscopic study of pairs of neutral and charged quantum dots where coherent coupling between the dots can be induced by a combination of electric field resonances and optical excitation. The main spectroscopic features can be recovered with a relatively simple molecular model.

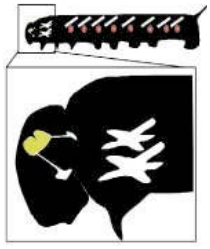
Under Pressure to Separate

When hydrogen is produced industrially, the gas stream is typically contaminated with H_2S, CO_2, steam, and other impurities that need to be removed. Ideally, the separation should occur at high pressure to avoid costly recompression, but current membrane materials do not work well at high pressure. **Lin *et al.*** (p. 639) have developed polymeric membrane materials that preferentially absorbed CO_2 and other impurities and that showed greater efficiency as the pressure of the gas feed was increased. Unlike conventional membranes, the presence of impurities plasticizes the polymer membranes and improves their selectivity and permeability.

Differences Without Diversity

When adapting to varied environments, some plants and animals take on alternative phenotypes but retain the same genotype. The classic laboratory model organism, the tobacco hawkmoth *Manduca sexta*, is monophenic with a green larval phenotype. However, the sister species, the five-spotted hawkmoth *M. quinquemaculata*, is polyphenic with a black phenotype at 20°C and green phenotype at 28°C. **Suzuki and Nijhout** (p. 650; see the news story by **Pennisi**) sensitized [illegible] Presents, Thx for Support





tal temperature by using a *black* mutant line. Mutation of the *black* gene reduced juvenile hormone and increased melanization of the larval epidermis. Heat shock of the *black* mutant generated larva with colors ranging from black to green. Two lines were established with the desired phenotype (green or black) by selecting individuals from subsequent generations of black mutant populations. Polyphenism can thus evolve by genetic accommodation regulated by juvenile hormone.

Hydrogenation with Less Guidance

The selective addition of hydrogen across carbon-carbon double bonds to generate homochiral products is used to prepare a wide range of compounds, both in the lab and in industry. However, the scope of this reaction is often limited by the need for a specific group adjacent to the olefin, whether a phenyl or a coordinating oxygen or nitrogen substituent, to direct the catalyst. **Bell *et al.*** (p. 642, published online 8 December 2005; see the Perspective by **Wills**) show that a class of iridium compounds, coordinated by chiral ligands with both phosphinite and pyridine groups, can catalyze the asymmetric hydrogenation of olefins bearing only simple alkyl substituents. They reduce a vitamin E precursor at two noncontiguous C=C bonds in an alkyl chain with net selectivity exceeding 98%.

Continued on page 575

CREDITS (TOP TO BOTTOM): DI TORO *ET AL.*; SUZUKI AND NIJHOUT

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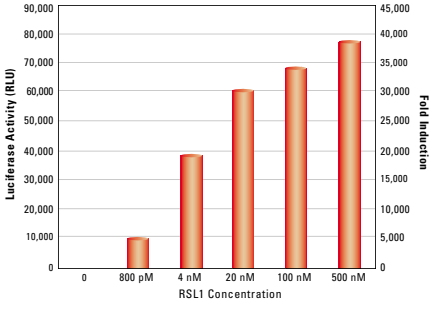

Luciferase expression in response to increasing RSL1 concentrations. NIH3T3 cells co-transfected with pNEBR-R1 and pNEBR-X1 expressing firefly luciferase were induced with the indicated RSL1 concentrations. Expression was measured 48 hours post-induction.

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Continued from page 573

Neurons Navigate Downstream

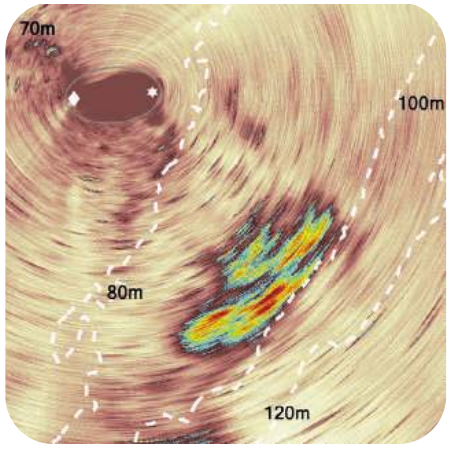
Neurons born near the brain's ventricles travel out to the olfactory bulb to function in olfaction. A steady stream of migrating neurons makes the journey not only in early development, but also during adulthood. **Sawamoto *et al.*** (p. 629, published online 12 January) now provide insight into how these neurons find their way in mice. The ventricles of the brain are lined with cells bearing cilia on their surface. The coordinated beating of these cilia develops a stream of fluid coursing through the ventricles carrying signaling factors that guide the traveling neurons. Mutations that disrupt the cilia also disrupt establishment of the signaling gradient and the migration of the neurons to the olfactory bulb.

Flexible RNA

Conformational flexibility of RNA molecules arises from a complex set of local motions, collective domain motions, and overall rotational diffusion. **Zhang *et al.*** (p. 653) describe a domain-elongation strategy that allows them to resolve picosecond local motions and nanosecond domain motions by nuclear magnetic resonance (NMR) spectroscopy. By comparing the structural dynamics to the conformational differences evident in eight HIV-1 transactivation response element structures, they show that a hierarchical network of local and collective internal motional modes underlies RNA's ability to change conformation adaptively.

Keeping Tabs on Schools of Fish

A technology for continuously monitoring fish populations over areas on the scale of continental shelves has been developed by **Makris *et al.*** (p. 660) that uses the ocean as an acoustic waveguide. Its areal survey rate is several orders of magnitude greater than that of current survey methods. The technology has been used to provide instantaneous images of enormous fish shoals in their entirety, as well as to reveal rapid temporal and spatial changes in these shoals.



CREDIT: MAKRIS *ET AL.*

HIV Decline in Zimbabwe

The human immunodeficiency virus epidemic in Zimbabwe is slowing down because of a large-scale change in sexual behavior, particularly among young and educated people. **Gregson *et al.*** (p. 664; see the Perspective by **Hayes and Weiss**) present an analysis that disentangles decline from the mortality of high-risk subpopulations and a lower infection rate of young people. These trends may be taking place across much of sub-Saharan Africa and seem to result from a combination of national program activities, condom use, and increased fear of death from AIDS.

Smelling in Stereo

Stereo sound localization uses both intensity and phase differences between the ears to determine source direction. **Rajan *et al.*** (p. 666) report that olfaction can use similar cues. Trained rats can locate an odor source to the left or right using concentration differences or time-of-arrival differences. Rats can perform this task within a single sniff. Olfactory bulb neuronal responses recorded in response to directional odor stimuli were highly selective for the direction of odor stimulation.

Processing Nothing But Faces

Are there areas in the brain that are solely dedicated to the processing of faces? **Tsao *et al.*** (p. 670; see the Perspective by **Kanwisher**) used functional magnetic resonance imaging on monkeys in order to identify areas responding to faces, and then implanted electrodes in the principal area in order to identify its properties at the single-cell level. In this region, virtually all of the cells only responded to faces. This finding supports the idea that the cortex has a modular architecture.

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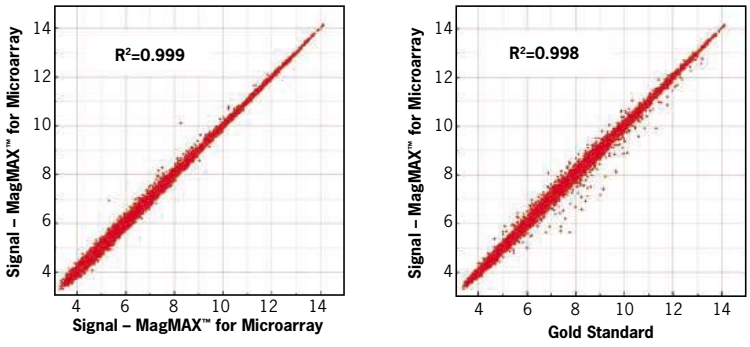

Scatter plot of normalized signal intensities of two mouse kidney total RNA samples using MagMAX™-96 for Microarrays and the Gold Standard. The correlation between samples is 0.999. The correlation between the two methods is 0.998. Greater than 60% percent Present calls were obtained for each method.

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Alan I. Leshner is chief executive officer of AAAS, executive publisher of *Science*, and a member of the GRC Board of Trustees.

Advancing the Frontiers

THERE HAS BEEN MUCH DISCUSSION RECENTLY ABOUT WAYS TO STIMULATE MORE "HIGH-RISK–high-payoff" research: projects that have the potential to make major leaps in scientific understanding. In the United States, the National Science Board, for example, has had a task force dedicated to this issue for over a year, and the National Institutes of Health's Roadmap includes efforts to transform fundamental and clinical biomedical research.

One approach to advancing these frontiers has proven quite successful over the years. It is the model used by the Gordon Research Conferences (GRCs), which this year celebrate their 75th anniversary; their 2006 program appears in this issue of *Science*. The GRCs, which began in 1931 as a chemistry meeting conceived and organized by Neil Gordon, now encompass some 180 conferences each year at 17 different sites in the United States and abroad. Over 20,000 international scientists will participate in these intense meetings that span the whole spectrum of science, science education, and science policy. The American Association for the Advancement of Science (AAAS) has had a close association with the GRCs since 1938, when it took over managing the conferences—an arrangement that lasted until 1956, when the GRCs became independent.

A fascinating compendium* of personal reminiscences about the conferences and their scientific impacts, contributed by a diverse group of 80 well-respected scientists, reveals why these conferences are so popular and successful and why they have persisted on a regular basis for so long. Reduced to its core, the success of these meetings amounts to the way in which their format has promoted transformative thinking and project development. Maxine Singer, for example, writes about the importance of the 1973 Nucleic Acids meeting in stimulating thinking about the implications of recombinant DNA (cloning) experiments. Other authors cite the central role of the GRCs in the emergence of such multidisciplinary fields as bioinorganic chemistry, organic electronics, and mammary gland biology.

A core lesson from the GRCs is that even in this age of electronic communication technologies, there is no substitute for putting a small group of people together face to face and keeping them in close contact for a few days. The relatively isolated sites used for the GRCs and the fact that each conference is usually restricted to about 100 attendees encourages people to talk to each other with both informality and candor. And the conference agenda allows for plenty of unstructured discussion time and promotes long conversations about frontier science.

Many of the important unanswered scientific questions are multidisciplinary in character. This feature of contemporary research was amply demonstrated in *Science*'s 2005 list of the top 25 questions for the next 25 years.† To promote the kind of thinking needed for problem-based rather than discipline-based science, one needs to bring experts together from all potentially relevant fields and create an environment in which they may speak freely and frankly with one another. That is exactly the kind of conversation that GRC attendees are engaged in. All discussions are off the record, and all conference communications are considered private. This fosters safe spaces for posing "risky" ideas and engaging in creative and occasionally speculative communal thinking. As Norman Hackerman emphasizes in the GRC compendium, "The greatest advantage of these meetings was that attendees were able to participate without worrying about being proved wrong in publication . . ." On the nonhierarchical nature of the meetings, Roy Vagelos reflects, "There I was [at his first Lipid Metabolism conference], a pipsqueak only a few years out of a postdoctoral fellowship, speaking alongside these giants of biochemistry." Not surprisingly, some of the giants later became Vagelos' collaborators.

The GRCs are only one way to encourage transformative thinking and research, but their track record suggests that we may need more venues like them. Scientists sometimes lament that peer review may be biased in favor of cautious and "safe" research, unsupportive of departures from mainstream thinking. By creating a relatively unthreatening, unconstrained atmosphere, the GRCs provide a refreshing opportunity to try out new ideas on one's colleagues, brainstorm about difficult and complex issues, and think about possible solutions. Not a bad strategy at all.

–Alan I. Leshner

10.1126/science.1125130

Reflections from the Frontiers, Explorations for the Future: Gordon Research Conferences, 1931–2006*, A. A. Daemmrich, N. R. Gray, L. Shaper, Eds. (Chemical Heritage Press, Philadelphia, PA, 2006). †*Science* **309, 75 (2005).

CREDIT: GORDON RESEARCH CONFERENCES

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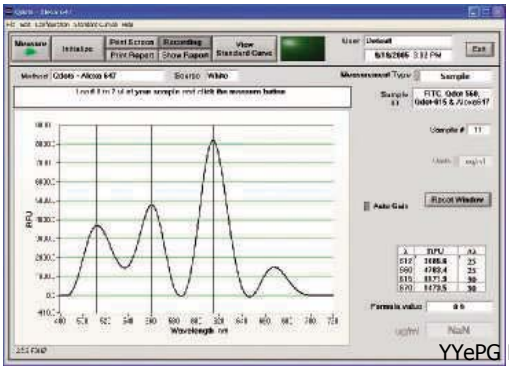

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HIGHLIGHTS OF THE RECENT LITERATURE

ECOLOGY/EVOLUTION

Regulating Food Intake


The kakapo.

The kakapo—a bulky, ground-dwelling parrot endemic to New Zealand—is one of the world's most endangered birds, with just 83 living individuals. For the past 15 years, conservationists have attempted to increase the population by the supplementary feeding of female birds. However, although ad libitum feeding has indeed improved chick survival, it has also changed the sex ratio of offspring hatched, so that 70% of chicks are male: a proportion clearly at odds with conservation objectives.

Offspring sex ratio is known to be affected by environmental factors and maternal conditions in predictable ways; in particular, females in good condition tend to produce more sons. Robertson *et al.* have recently achieved near-parity in offspring sex ratio by regulating the amount of supplementary food given to females as a function of their predicted weight; feeding could not be abandoned entirely, because female kakapo need to weigh more than 1.5 kg in order to breed at all. Thus, the prospects for a conservation program have been enhanced by the application of theory from evolutionary biology. — AMS

Biol. Lett. 10/1098/rsbl.2005.0430 (2006).

APPLIED PHYSICS

THz in Practice . . .

Terahertz (THz) radiation penetrates cloth and plastic to a degree that scales inversely with the frequency. Solid-state laser sources, such as quantum cascade lasers, have been fabricated with energy-level separations tuned for emission toward the high end of the THz regime. However, efforts to lower the frequency, and thereby improve penetration, have been hindered by scattering problems and by reduced out-coupling efficiency as the energy-level spacing approaches the emission linewidth.

Worral *et al.* demonstrate a superlattice quantum cascade laser that emits 2-THz continuous wave radiation at an operating temperature of 47 K. They accessed this low-frequency region in part by precise modulation of the aluminum doping level in the GaAs/AlGaAs lasing medium. The result suggests that the emission frequency might be reduced further by careful control of the fabrication and design process. — ISO

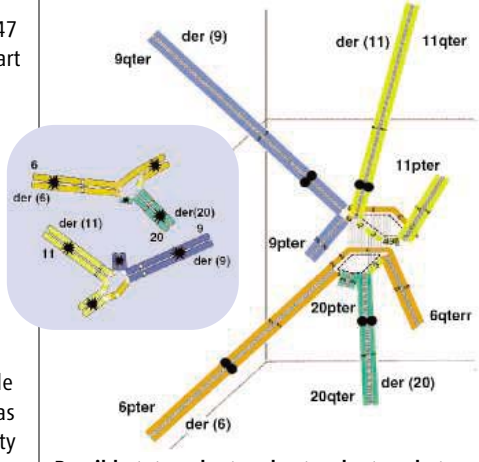
Opt. Exp. **14**, 171 (2006).

GENETICS

A Familial Four-Way Swap Fest

Qualitative advances in technology have made it possible to reexamine an old case, which has led to a heightened appreciation of the fidelity of chromosomal segregation. Over 2 decades ago, a patient with a history of miscarriage was analyzed with classical cytogenetic techniques, yielding evidence of a complex rearrangement involving chromosomes 6, 9, 11, and 20. Later, the mother carried a fetus to term; the adult daughter was determined to carry the same rearrangement and, like the mother, displayed modest levels of the fetal form of hemoglobin [hereditary persistence of fetal hemoglobin (HPFH)].

Fauth *et al.* have used multiplex fluorescence in situ hybridization and DNA microarrays to map the precise nature of the rearrangements. They find that the derivative chromosome 6 [referred to as der(6)] possessed by mother and daughter contains portions of chromosomes (chrs) 11 and 20, der(11) carries bits of chrs 6 and 9, der(20) contains portions of chrs 6 and 11, and der(9) harbors multiple pieces from chrs 6 and 11, adding up to a total of 12 breakpoints (one of which coincides with a quantitative trait locus for HPFH) spread over four chromosomes. Nevertheless, these rearranged chromosomes pass faithfully through the pachytene stage of meiosis, when homologous chromosomes pair and form bivalents. — GJC



Possible tetravalent and octavalent pachytene configurations.

Hum. Genet. 10.1007/s00439-005-0103-z (2006).

IMMUNOLOGY

Primed by Parasites

Collectively, parasites belonging to the genus *Leishmania* cause extensive mortality and morbidity around the globe. Two major forms of leishmaniasis are characterized by distinct pathologies: a life-threatening visceral disease and a cutaneous form, involving self-healing skin ulcerations. In the latter, resident macrophages and dendritic cells (DCs) of the skin take up the parasite, although in DCs this leads to the priming of T_h1 cells that ultimately resolve the disease.

Woelbing *et al.* show that unlike macrophages, which use the complement receptor to bind and phagocytose *Leishmania* promastigotes, DCs acquire the parasite through Fc receptor (FcR)–mediated uptake of complexes comprising

Continued on page 581

The ability to perceive or think differently is more important than the knowledge gained.

David Bohm
American scientist (1917-1992)

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Continued from page 579

antibodies to *Leishmania* bound to parasitic amastigotes. Without B cells, normally resistant mice became susceptible to disease, as did animals genetically lacking the relevant FcR for IgG binding. In both cases, disease susceptibility was directly attributable to a failure of DCs to prime T cells efficiently and, consequently, to reduced production of IFN-γ. This pivotal role for antibodies to parasites in the priming of T cell immunity by DCs raises the interesting question of how the initial B cell response to the parasite itself develops. — SJS

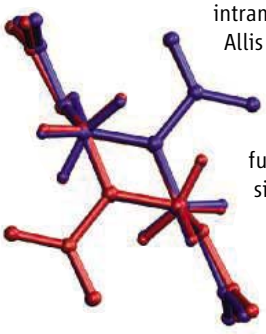
J. Exp. Med. 10.1084/jem.20052288 (2006).

CHEMISTRY

. . . and in Theory

Terahertz (Thz) radiation, which bridges the infrared and microwave regions of the electromagnetic spectrum, can penetrate most clothing and packaging materials. Researchers have therefore sought to develop THz spectroscopy for security screening, which would require a precise understanding of the absorption spectra that would signal the presence of drugs or explosives. However, the spectra are hard to analyze because they comprise many overlapping modes, arising both from intramolecular vibrations and delocalized lattice motion.

One approach has been to model the individual molecules computationally, as though they were in the gas phase, in order to discern which spectral features correspond to intramolecular modes, but Allis *et al.* uncover a problem with this method. Using several variants of density functional theory, they simulate the THz absorption spectrum of crystalline HMX explosive, a solid composed of eight-membered rings with alternating CH_2 and $N(NO_2)$ groups. Modeling of the isolated molecule fails to reproduce any of the experimental absorption features, whereas more computationally demanding methods, which treat the extended solid lattice, yield reasonable agreement with the measured spectrum. The results suggest that packing forces in the lattice shift the orientation of NO_2 substituents and thereby affect intramolecular mode frequencies in addition to lattice modes. — JSY



Calculated geometries of HMX: gas-phase (red) and solid-state (blue).

CREDITS: ALLIS *ET AL.*, *J. PHYS. CHEM. A* 10.1021/JP0554285 (2006)

J. Phys. Chem. A 10.1021/jp0554285 (2006).

BIOMATERIALS

Mixing and Matching

Strategies for spinal cord injury repair may benefit if a more controlled delivery of drugs to the site of the wound can be achieved. Although bolus injection or a minipump can be used, with the former, the drug may wash away, and a catheter may become blocked or infected. One approach would be to encase the drug in a biodegradable gel that has a viscosity low enough for injection and that gels fast enough to localize to the wound, while being biocompatible and nonadhesive.

Gupta *et al.* have designed such a material by combining methylcellulose (MC) and hyaluronan (HA). HA is known to promote wound healing by reducing inflammation and minimizing tissue adhesion. However, it is highly soluble in water and disperses when injected into fluid-filled cavities. MC has inverse gelling properties—that is, it gels as the temperature rises by breaking polymer-solvent bonds and forming hydrophobic junctions. A mixture of 2% HA and 7% MC had a low viscosity and showed fast gelling and suitable degradation characteristics. Intrathecal injection in rats showed that the gel performed as well as or better than artificial cerebrospinal fluid. — MSL

Biomaterials **27**, 2370 (2006).

GENETICS

Four Score and Nine Generations Ago

Neurodegenerative disorders vary in their pathologies, but because they all involve cell death, there is the possibility that they share a common mechanism of pathogenesis. One emerging hypothesis posits that the disorders arise because of defects in the intracellular machinery that transports vesicles and proteins.

Ikeda *et al.* have studied three families afflicted with spinocerebellar ataxia type 5 (SCA5), a dominantly inherited neurodegenerative disorder characterized by uncoordinated gait and slurred speech. Affected individuals were found to have mutations in the *SPTBN2* gene, which encodes β-III spectrin, a cytoskeletal protein that is expressed in Purkinje cells, which are markedly depleted in the brains of individuals with SCA5. β-III spectrin has been implicated previously in protein trafficking, and the mutations may disrupt transport of the neurotransmitter glutamate. Of historical interest, one of the families studied was an 11-generation kindred descended from the paternal grandparents of President Abraham Lincoln. Whether he inherited the SCA5 mutation is unknown, but this discovery may reignite discussions on the ethics of analyzing his DNA. — PAK

Hum. Mol. Genet. 10.1093/hmg/ddl021 (2006).

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Information for Contributors

See pages 102 and 103 of the 6 January 2006 issue or access www.sciencemag.org/feature/contribinfo/home.shtml

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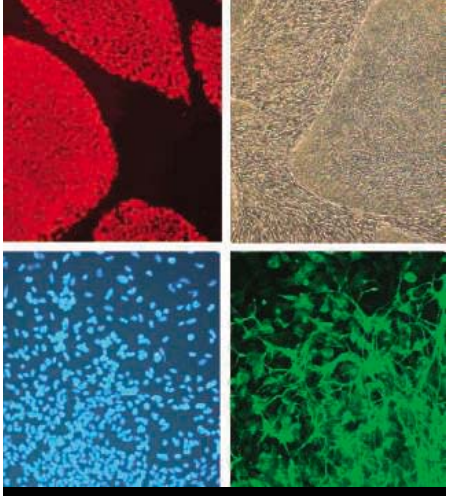


COMMUNITY SITE

STEM CELL CENTRAL

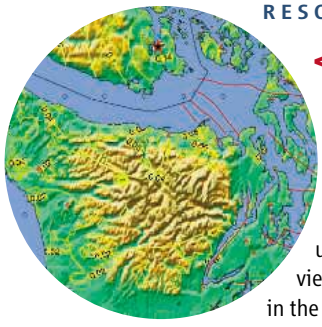
Human embryonic stem cells excite researchers because they can theoretically diversify into any tissue in the body. But the existing stem cell lines were grown under a variety of conditions—some came from frozen embryos, some didn't, for instance—that could affect their performance. Researchers can nab up-to-date information on available lines at the Stem Cell Community, a year-old site from the Burnham Institute in San Diego, California. After completing the free registration, visitors can scan a database that describes more than 240 stem cell lines, including 53 approved for study with U.S. government funds. Users will find information such as where the cells came from, what protein markers they sport, whether they've ever been frozen, and whether they were nurtured with mouse feeder cells. Site co-curator Jeanne Loring says that to fill out the cell portraits, she and her colleagues are gathering microarray measurements of gene activity, data on genetic variability, and other information. The site also includes a Community Information section where you can track down courses on rearing stem cells or peruse a news archive. >> www.stemcellcommunity.org

WEB LOGS

Opinion Buffet

Craving a discussion of the greatest physics experiments of all time? Hungry to know how computer-generated animation can more realistically depict emotions? Tuck into this new blog smorgasbord from *Seed* magazine. The site serves up 15 scientific and science-related columns on topics as diverse as research ethics, evolutionary biology, and disease. Contributors include a cognitive scientist and her husband, a tenure-track physicist, and a former Senate staffer with a Ph.D. in geophysics. >> scienceblogs.com

RESOURCES



<< Quaking 'Round the Clock

This newly upgraded seismic monitoring site from the U.S. Geological Survey (USGS) will shorten the delay for obtaining earthquake data. USGS's National Earthquake Center now has researchers on duty around the clock to help speed measurements to the Web. Before, impatient users sometimes had to wait up to 2 hours after a quake to view online reports, but now information on temblors anywhere in the world will post within 30 minutes, says Webmaster Lisa Wald. Click on U.S. or global maps to find out the depth, strength, and location for events within the past week. Other report features include seismic hazard maps that indicate the peak ground acceleration during the quake. Visitors can dig up plenty of other information on recent and historic quakes. This shake map (above), for instance, depicts the maximum ground velocity after a magnitude 3.3 temblor last month near Victoria, Canada. >> earthquake.usgs.gov

TOOLS

Tracing Genetic Wrongdoers

Geneticists have pinpointed the genes responsible for diseases such as cystic fibrosis, but for other illnesses, researchers only know the chromosome region where the gene lurks. GeneSeeker from Radboud University in Nijmegen, Netherlands, can help narrow the list of potential culprits. The search engine combs 10 databases that contain information on gene location, activity, and effects, including Online Mendelian Inheritance in Man, Swiss-Prot, and the Mouse Genome Database. Users pick a chromosome location linked to a condition, such as cataracts or cleft palate, and then specify an organ or structure in which the gene should be active. The results list genes that match the criteria, along with near misses, such as genes that fall in the right region but don't show the correct expression pattern. >> www.cmbi.ru.nl/GeneSeeker/

RESOURCES

Mammals in Print

Since 1969, the American Society of Mammalogists has published 20 to 30 species accounts each year that cover taxonomy, anatomy, ecology, and other aspects of the animals' biology. At this site from series editor Virginia Hayssen of Smith College in Northampton, Massachusetts, you can download PDFs of these definitive references for more than 700 species. The animals featured include the snow leopard (*Uncia uncia*) of central Asia and the naked mole rat (*Heterocephalus glaber*; right) of eastern Africa, which dwells in colonies similar to those of bees and ants. >> www.science.smith.edu/departments/Biology/VHAYSSEN/msi/msiacounts.html

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Eurasian griffon vultures.

VULTURE CULTURE

Large congregations of vultures are once again appearing in the western Indian state of Rajasthan—a welcome sight after a precipitous, decade-long decline, allegedly from poisoning by an anti-inflammatory drug ingested from dead cattle (*Science*, 8 October 2004, p. 223). Conservationists in India have been clamoring for a phaseout of the sale of the drug, diclofenac, for veterinary use. Vibhu Prakash, head of the Vulture Care Centre at Chandigarh, says large new populations of griffon vultures, apparently migrants from Europe and Mongolia, do not appear to be affected yet, but he believes "it is merely a matter of time."

But scientists led by zoologist Rhys E. Green of Cambridge University in the U.K. say there may be a way out. They gave 35 captive-bred vultures in South Africa and India meat laden with a different anti-inflammatory drug, meloxicam, available for use in cattle. In the March issue of *PLoS Biology*, they report that the drug appears to be safe for vultures.

FROM PREDATOR TO PAL

Scientists have long debated just when canines and people started being such great chums. Most genetics-based estimates indicate that the domestic dog line split from its predecessor, the gray wolf, sometime between 15,000 and 40,000 years ago.

Darcy Morey, an archaeologist at the University of Kansas in Lawrence, argues that dog burials are a much better indicator of domestication. Morey combed the literature for evidence of ancient dog graves and identified more than 50 sites where dogs were buried singly, in packs, or even cuddled up with people. The earliest known dog burial, 14,000 years old, was in Germany; others, in Siberia, date back 10,650 years, Morey reports in the February issue of the *Journal of Archaeological Science*. The earliest North American site, at Koster, Illinois, is 8500 years old.

5000-year-old Kentucky burial.

Morey concludes that domestication most likely began about 14,000 years ago. Simon Davis, a zooarchaeologist at the Portuguese Institute of Archaeology in Lisbon, is convinced. DNA studies may tell us when doggy ancestors split from the wolf line, he says, but not when faithful mutts started curling up by the campfire.

Carles Vilà, a geneticist and evolutionary biologist at Uppsala University in Sweden, agrees that "genetic divergence is not the same as domestication," but he suspects that dogs were tamed long before they started being ceremonially interred. Morey disagrees, saying the "essence" of domestication is "a social relationship that is clearly signified" by the burials.

MAKE HER LAUGH

Most people agree that a sense of humor is desirable in a mate. But a study in the January issue of *Evolution and Human Behavior* indicates that women find this trait much more important than do men.

Evolutionary psychologist Eric Bressler of Westfield State College in Massachusetts and behavioral ecologist Sigal Balshine of McMaster University in Hamilton, Canada, showed 210 undergraduates, 105 of each sex, photos of two equally attractive members of the opposite sex along with eight statements supposedly made by each. For one, all eight statements were not amusing ("Every year I go to a cabin that my uncle owns, and I go cross-country skiing"). For the other, three were humorous ("I like the lottery because it's basically a tax on people who are bad at math"), and five were not. Students were asked to rate the two subjects on characteristics such as intelligence, trustworthiness, and romantic desirability.

Desirable catch?

Female students overwhelmingly deemed the humorous males more desirable. But the males were not swayed either way by funny women. Evolutionary psychologist Geoffrey Miller of the University of New Mexico in Albuquerque says humor is "a hard-to-fake indicator of several important traits: intelligence, creativity, and mental health." But for many men, who are more visually oriented in matters of sex, he says, beauty still trumps wit.

Fire and Ice

Lava and ice couldn't be farther apart on the thermal spectrum, but when it comes to carving up mountains, the two have a lot in common. In the 20 January issue of *Physical Review Letters*, researchers show that—during a 2001 volcanic eruption on Sicily's Mount Etna—lava carved a channel 6 meters deep in a mere 12 hours. That's far too fast for the gully to have melted, meaning the lava plowed its way through the rock much as a glacier would. The researchers say the results may provide new understanding of how ancient lava flows dug the large channels on Venus and the moon.

Lava channel on Mount Etna.

CREDITS (TOP TO BOTTOM): PALLAVA BAGLA; HO/REUTERS; GEORGE CROTHERS, WILLIAM S. WEBB MUSEUM OF ANTHROPOLOGY, UNIVERSITY OF KENTUCKY, LEXINGTON; C. FERLITO AND J. SIEWERT

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SCIENCE EDUCATION

Strategies Evolve as Candidates Prepare for Kansas Board Races

LAWRENCE, KANSAS—Billboards touting everything from steak to flat-screen TVs assault drivers speeding along I-35 across the American Midwest. But an unusual sales pitch pokes out of the ground just as the interstate leaves Missouri and enters Kansas. "Evolution is a fairy tale for grown-ups," the sign proclaims, steering viewers to a Web site that mocks the idea that evolution can explain the origin of human beings.

That Web site (scienceprovesit.com) is a stark reminder of what scientists and educators face as they battle new state science standards casting doubt on evolutionary theory and effectively opening the door to intelligent design (ID) and creationist instruction in Kansas public schools. The terms of four of the six-person majority on the state school board that adopted those standards 3 months ago end this year, and defenders of evolution hope voters will choose moderates in their place who will work to have those standards thrown out. Last weekend, a rally in Lawrence by Kansas Citizens for Science (KCFS) served as a de facto kickoff to these candidates' campaigns.

But moderates hoping to unseat the incumbents say a frontal assault on the new standards would be self-defeating in a state where conservative voters may sympathize with ID even though they have no appetite for the fundamentalist, right-wing groups that have led the charge against evolution. Instead, they plan to attack other board actions that they believe are unpopular with voters, including state-funded vouchers for private schools and a newly appointed education commissioner whose qualifications have been questioned. They also hope to draw on the recent U.S. District Court ruling that threw out ID language inserted by the Dover, Pennsylvania, school board, calling the attempt an unconstitutional intrusion of religion into the classroom and ordering it to pay what are expected to be significant legal fees.

Legal talk. Lawyers for the Dover, Pennsylvania, plaintiffs joined Kansas Citizens for Science in Lawrence last week in attacking the state's new science standards.

"If I were to make the new science standards the focus on my campaign, it's very likely that I would lose," says Harry McDonald, a former biology teacher who is running against incumbent John Bacon, who voted for the new standards, in the 1 August Republican primary. Republican Sally Cauble, a former elementary school science teacher contesting a seat held by strident ID supporter Connie Morris, echoes the thought. "You have to watch out for that strong undercurrent of support for faith-based education, including intelligent design," she says. McDonald and Cauble say they won't hide their pro-evolution stance but that they'd prefer to have voters raise the issue. "It's not mentioned in any of my campaign materials," says Cauble.

Supporters of evolution admit grudgingly that ID proponents have successfully framed the issue as a battle between science and religion. "It's a tricky line for the candidates to navigate," says KCFS's Jack Krebs, who spoke at the Lawrence meeting alongside lawyers representing the Dover parents who prevailed in December (*Science*, 6 January, p. 34). "Since sophisticated discussions on evolution and religion are not common in our society," Krebs says, "it's very easy for right-wing groups to brand the challengers as godless atheists."

A former president of KCFS who now conducts workshops for science teachers and cultures butterfly larvae to donate to schools in his district, McDonald takes care not to come across as a passionate evolutionist. His literature mentions the new standards as an example of micromanagement by the current board, which took over the writing of the standards last year after rejecting a draft submitted by the science standards writing committee. "There are ID sympathizers in my constituency who might be willing to forgive me my transgressions for being a strong science supporter because of other issues. But if I spent too much time on evolution and ID, they might not."

Bacon told *Science* he hasn't decided whether to seek reelection to another 4-year term. But he says that, should he run, he would have no qualms advertising his role in promoting the new standards, even though it would not be a centerpiece of his campaign. "I've seen polls showing that the majority of people in the state want their kids to be exposed to ▶

Battlefield Kansas. State school board candidate Harry McDonald faces a challenge from antievolution groups such as the sponsors of this billboard.

CREDITS: Y. BHATTACHARJEE/*SCIENCE*

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all theories of origin science in the classroom," he says. "If evolution is a theory, they want it taught as a theory, not as a fact."

Both sides agree that, to the extent that evolution gets discussed during the electoral race, the Dover decision will certainly help the challengers. But John Calvert, the managing director of the ID Network in Shawnee Mission, says it would be unfair to compare the actions of the two boards. "The Kansas standards do not require the teaching of ID in the classroom," he says. "What they do is give teachers the freedom to answer critical questions about evolution without fear of being leaned on."

Don Weiss, a dean at DeVry University in Kansas City and a Democratic challenger who would face Bacon in November should both win their primary races, says he intends to use the financial aspect of the Dover ruling as ammunition. "Either we can have a very expensive lawsuit, or we can get it taken care of through the election," Weiss says he'll tell voters. But then he'll reclaim the high ground. "My broader message is going to be about improving the quality of education in Kansas, so that our kids can compete in a global economy."

–YUDHIJIT BHATTACHARJEE

PLANETARY SCIENCE

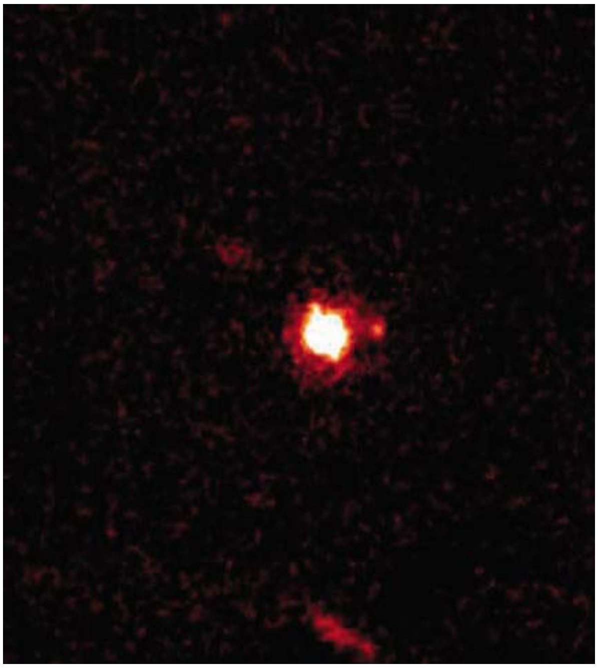
New Hubble Image Cuts the "10th Planet" Down to Size

LOS ALTOS HILLS, CALIFORNIA—Confounding previous estimates, the so-called 10th planet is Pluto's near-twin in size, according to a new image from the Hubble Space Telescope. The object is just a "smidge" bigger than Pluto, not 25% to 50% bigger, an astronomer reported here last week, and unusually reflective. The downsizing illustrates the quandary facing scientists as they try to define whether large residents of the frigid Kuiper belt are bona fide planets.

Planetary scientist Michael Brown of the California Institute of Technology (Caltech) in Pasadena and colleagues found the object, designated 2003 UB313, as a slow-moving dot of light. It traces an elongated orbit out to its current farthest point of 97 times Earth's distance from the sun, making it the most remote body yet seen in our solar system. Despite its distance, the object dubbed "Xena" by Brown's team appears so bright that last July NASA described it as markedly larger than Pluto (*Science*, 5 August 2005, p. 859). But researchers sought better data to gauge its true size.

One new study, published this week in *Nature*, favors a chubbier Xena. A team led by radio astronomer Frank Bertoldi of the University of Bonn, Germany, used the IRAM 30-meter radio telescope at Pico Veleta, Spain, to measure the object's heat emissions. Their analysis points to a diameter of 3000 kilometers, compared to 2300 kilometers for Pluto—but with substantial error bars.

Such errors are far smaller with a direct view from orbit, Brown says. The Hubble Space Telescope zeroed in on Xena in December 2005. Brown showed the newly analyzed image to about 1000 people at a public lecture here at Foothill College. The blob of light, spanning several pixels on Hubble's detector, had enough resolution for Brown's team to determine that Xena is barely bigger than Pluto. Brown said he would reveal the calculated size at a NASA press briefing. For now, he said, "I'm going to stick with the word 'smidge.' It's a really good word."



Pluto plus. Distant "Xena"—shown in a ground-based image with its small moon—is barely bigger than Pluto, a new Hubble photo reveals.

CREDIT: A. BOUCHEZ, M. VAN DAM, D. LE MIGNANT/W. M. KECK OBSERVATORY LASER GUIDE STAR ADAPTIVE OPTICS TEAM

But the size was evident from a statistic shown by Brown: Xena reflects a remarkable 92% of optical light, like the finest fresh snow. "I had expected it to be darker and considerably larger," Brown said. This measure, called albedo, is derived from the object's apparent brightness, distance, and diameter. According to a chart on Brown's Web site, that diameter is roughly 1% larger than Pluto's—down from the team's previous guesses of 25% larger (on the Web site) to 50% larger (at NASA's July announcement).

Icy bodies darken with age, so geysers must recoat Xena's surface with fresh frost, Brown said. Planetary scientist David Stevenson of Caltech notes that Saturn's active moon Enceladus is the only other object in the solar system that glistens as radiantly. But Enceladus flexes during its eccentric orbit around Saturn, generating enough heat to expel icy compounds from the moon's interior. There's no obvious way to spark such action on Xena—even with its small moon. "Frankly, volcanism in the Kuiper belt is hard," Stevenson says. "Maybe we don't understand the dynamics of crystallization and the physics of ice surfaces."

Nor will Xena help the messy debate over planet nomenclature. Late last year, a working group of the International Astronomical Union (IAU) failed to agree on any of three proposed "planet" definitions and passed the buck to IAU's executive committee. Astronomers are finding so many planet-like objects—both in our solar system and around other stars—that the prudent course may be to wait instead of forcing a hasty consensus, says committee member Robert Williams of the Space Telescope Science Institute in Baltimore, Maryland.

Although people are loath to demote Pluto from planethood, they may not want dozens of Pluto-size "planets" either, says Foothill astronomer Andrew Fraknoi. "It's almost cosmic justice" that Xena and Pluto are a near-match, he says. "Welcome to the borderland of science."

–ROBERT IRION

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EVOLUTION

Hidden Genetic Variation Yields Caterpillar of a Different Color

People change clothes depending on the temperature outside. Tomato hornworms change color. These caterpillars emerge green when it's above 28°C and black when it's cooler. Now two insect physiologists report on page 650 that they have teased out a possible genetic basis of this color change by breeding a mutant strain of a related species, the tobacco hornworm, until it too undergoes a similar switch.

The study demonstrates how species can mask effects of genetic mutations until an environmental trigger reveals them, an adaptive mechanism that may help organisms survive changing conditions. The work "is a tour de force of experimental evolutionary biology," says Mary Jane West-Eberhard, an evolutionary biologist at the University of Costa Rica. "It [begins] to answer a question of fundamental importance: How does a novel, environmentally sensitive trait originate?"

Fashion statement. Tobacco hornworms can evolve a finely tuned sensitivity to heat that causes them to emerge green instead of black.

CREDITS: Y. SUZUKI *ET AL.*, *SCIENCE*

Organisms that live in variable environments often evolve traits—called polyphenisms—that change according to particular conditions. Aphids become winged or wingless, for example, depending on food availability. The tomato hornworm's color change serves a similar adaptive purpose. In the cooler northern United States, the caterpillars that emerge in the autumn are black to absorb more sunlight, but in the south, where camouflage is more important than heat conservation, they're green. In contrast, tobacco hornworms are typically green, no matter the temperature.

The genetic underpinnings of polyphenisms have long been a puzzle, notes Douglas Emlen, an evolutionary biologist at the University of Montana, Missoula. To examine how the tomato hornworm's color-shifting may have arisen, Yuichiro Suzuki, a graduate student working with Frederik Nijhout at Duke University in Durham, North Carolina, turned to a tobacco hornworm mutant that is black rather than the normal green. Its mutation reduces secretion of juvenile hormone, which regulates skin coloring. This mutant strain, however, generates caterpillars with varying degrees of green if it is heat-shocked—briefly exposed to a very high temperature—at an early stage of development.

Suzuki used this heat-shock method to select for two spinoff strains. In one case, he mated only tobacco hornworm caterpillars that remained dark despite the heat shock, weeding out greenish ones each generation. By the seventh generation, this line, even after being heat-shocked, produced only black larvae. At the same time, Suzuki bred the caterpillars that developed the greenest skin when heat-shocked. Over time, this selection had dramatic results, creating a strain whose caterpillar form always emerges green instead of black if grown above a specific threshold temperature, 28.5°C.

The experiments indicate that low juvenile hormone levels in the original black mutant had enabled already-existing variants involved in pigment production to exert their effects, depending on the temperature. Normal tobacco hornworms have very high amounts of juvenile hormone, but Suzuki and Nijhout showed that the heat-insensitive version of the mutant strain had very little and the newly created polyphenic strain had levels in between. In this latter strain, higher temperatures resulted in more juvenile hormone and, consequently, greener skin. Suzuki and Nijhout propose that there may be other cases in which evolution has exploited developmental hormones to create polyphenic traits.

Evolutionary biologist Mark Siegal of New York University cautions that what happens in the lab isn't necessarily what happens in real life. But he applauds the study. "[This] laboratory demonstration is an important first step that will guide the crucial, and difficult, effort to understand actual evolutionary histories," he says.

–ELIZABETH PENNISI

Iranians Seeking Uranium

Negotiations over Iran's nuclear program may founder on one key issue, Vienna-based diplomats tell *Science*: whether Iranian researchers will be permitted to work side by side with Russians on uranium enrichment.

With Iran's referral to the U.N. Security Council looming as *Science* went to press, negotiators are pushing Iran to relinquish its right to enrich uranium. Under a Russian proposal, Russian centrifuges would boost the percentage of fissile uranium in Iranian hexafluoride gas. It's hoped that would deter Iran from using its own centrifuges to produce even higher percentages of fissile fuel for bombs. The plan, sources say, restricts Iranian scientists' presence at the facility to thwart leakage of knowledge that might accelerate Iran's alleged weapons program.

Iran has vacillated on the Russian proposal, and negotiations are expected to resume next week. Iran "will insist on learning more about enrichment technologies if the deal goes through," predicts Jack Boureston of nonproliferation research group FirstWatch International.

–RICHARD STONE

Fish Science Center Cast Off

In a controversial move, the Bonneville Power Administration (BPA)—the U.S. federal agency that oversees Pacific Northwest hydropower—has appointed new groups to count salmon returning to upstream spawning grounds. Last week, BPA announced that it will cut ties in March to the Fish Passage Center (FPC), an 11-person, $1.3 million operation that has long provided data to biologists who determine fishing seasons and salmon-recovery plans.

BPA will give fish-counting duties to the Pacific States Marine Fisheries Commission, with routine analysis to be done by Pacific Northwest National Laboratory. But Rebecca Miles of the Nez Perce Tribe, which has rights to the fish, says that now is the wrong time for changes, as comprehensive salmon-recovery plans are under negotiation. The move blocks access to "the best scientific data," she says. But the replacements say they're qualified, and BPA's Greg Delwiche says separating the data gathering from the analysis will strengthen the underlying science.

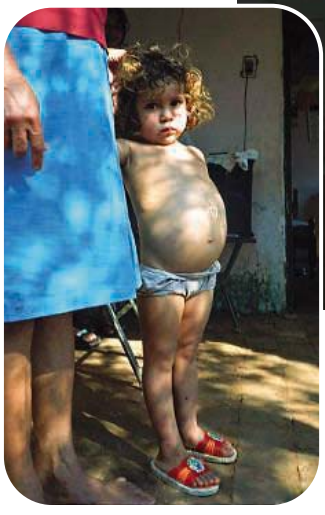
A federal judge cited FPC data last July when he ruled that additional water needed to be released from Columbia River dams, a move that cost BPA $79 million and triggered the ire of Senator Larry Craig (R–ID). He inserted a provision into a spending bill forcing BPA to jettison FPC.

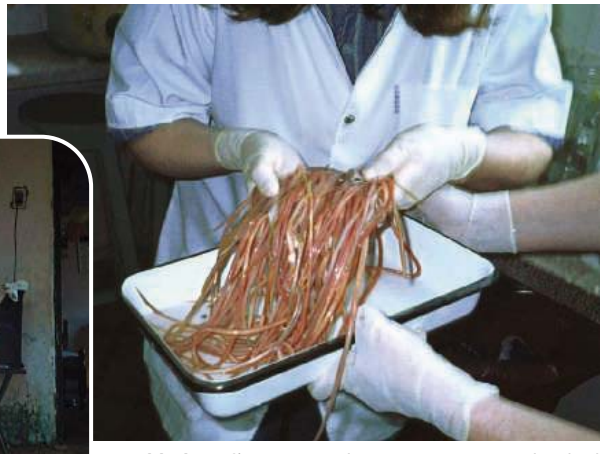
–ROBERT F. SERVICE

INFECTIOUS DISEASES

Tackling Neglected Diseases Could Offer More Bang for the Buck

STOCKHOLM—Public health efforts in the developing world are missing out on a bargain, say a group of researchers and health policy leaders. At a meeting here* and in a recent paper, they argue that the ramped-up efforts against the Big Three—HIV/AIDS, tuberculosis, and malaria—will yield far bigger dividends if they are coupled with an attack on so-called neglected diseases such as hookworm, schistosomiasis, and leishmaniasis. These infections make their victims more susceptible to the Big Three, the researchers contend.





Double benefit. Treating the ascariasis worms that had infected this girl (*inset*) may leave her less vulnerable to other diseases.

Up to seven neglected tropical diseases could be tackled for just 40 cents per person per year, they say. "It's the best buy in public health at the moment," says Alan Fenwick, a schistosomiasis researcher at Imperial College London.

Unlike HIV and malaria, lymphatic filariasis and onchocerciasis do not trip off the tongues of world leaders. Nor do such neglected diseases directly kill as many people as the Big Three. Instead, they take their toll more insidiously, through stunted growth, anemia, and blindness, contributing to widespread developmental and learning delays. These infections, both bacterial and parasitic, "are the world's leading cause of growth deficits and the world's leading education problem," says Peter Hotez, a parasitologist at George Washington University in Washington, D.C.

But neglected tropical diseases are vulnerable to a concerted campaign. Effective drugs—inexpensive or donated by drug companies—are available against many of them. And in a paper published 30 January in the *Public Library of Science Medicine*, Hotez, Fenwick, and their colleagues argue that treating the 500 million people afflicted would cost just $200 million a year—compared to $500 million pledged this year for antimalaria efforts.

At the same time, the authors argue, treating these seven diseases—the helminth infections ascariasis, trichuriasis, hookworm, lymphatic filariasis, onchocerciasis, and schistosomiasis, and the bacterial infection trachoma—might benefit the ongoing fight against the Big Three. They point to a growing body of evidence that suggests that populations infected with multiple parasites are more susceptible to other diseases—including the big killers.

The payoffs for malaria control might be especially worthwhile. Intestinal parasites are a leading cause of anemia—exacerbating one of the main complications of severe malaria. Hotez points to a study in Senegal that found that deworming medicines significantly reduced malaria cases.

There is also preliminary evidence that HIV patients infected with multiple parasites ▶

* U.N. Millennium Project: A Malaria and Neglected Tropical Diseases Quick-Impact Initiative, 30–31 January, Stockholm, Sweden.

GLOBAL WARMING

Climate Change Demands Action, Says U.K. Report

CAMBRIDGE, U.K.—As climate change climbs up the political agenda, researchers have pooled much of the most recent research into what many believe is a compelling case for the immediacy of global warming.

This week's report,* based on a meeting convened last year at the request of U.K. Prime Minister Tony Blair, warns of catastrophic consequences if steps are not taken now. It says a range of measures, from emissions trading to nuclear power, are needed to both minimize future impacts and cope with those that cannot be avoided. "It is clear from the work presented that the risks of climate change may well be greater than we thought," says Blair in a foreword to the report. "The U.K. government is taking this issue very seriously," says glaciologist David Vaughan of the British Antarctic Survey, "and it's nice to see the government consulting scientific opinion."

During 2005, Blair was both chair of the G8 leaders of industrial powers and president of the European Union and pledged to use his twin roles to combat global poverty and climate change. To advance the climate initiative, 200 researchers from across the globe met at the Hadley Centre for Climate Prediction and Research in Exeter last February. The meeting came 4 years after the last assessment report from the Intergovernmental Panel on Climate Change (IPCC)—the benchmark for global warming—and the scientists chewed over new results. "It was a good time to take stock," says steering committee chair Dennis Tirpak, head of the climate change unit at the Organisation for Economic Co-operation and Development in Paris.

According to the report, "Overall, compared to the [IPCC's 2001 assessment], there is greater clarity and reduced uncertainty about the impacts of climate change." The report contains models showing how the acidity of the oceans will increase as a result of more carbon dioxide in the atmosphere. It also forecasts a 1000-year rise in sea levels as a result of thermal expansion of the oceans and melting of the Greenland and Antarctic ice sheets, even if greenhouse gas emissions are stabilized. "Once peripheral melting is under way around Greenland," Vaughan says, "the ice sheet may enter a state where it can't sustain itself."

Tirpak says politicians need to realize that time is running out and that the next generation may live on a planet that has no icecaps in the summer months. "It will be a profoundly different world, and we cannot imagine what that will mean," he says. "Do you want to risk the consequences?" **–DANIEL CLERY**

* *Avoiding Dangerous Climate Change*, www.defra.gov.uk/environment/climatechange/internat/dangerous-cc.htm

CREDITS: PETER HOTEZ/GEORGE WASHINGTON UNIVERSITY

have higher viral loads and lower immune cell counts than their counterparts who are worm-free. And several studies have shown that worm infections can lessen the effectiveness of vaccines against other diseases. "Unless we do something about polyparasitism, we are not going to have a big impact on the Big Three," Hotez says.

On a practical level, the infrastructure for distributing deworming drugs could also be used to deliver antimalarial bed nets. The researchers hope to put their ideas into practice soon. At this week's meeting, researchers and public health leaders from eight African countries met to devise a "quick impact initiative" that would create national programs to tackle malaria and the neglected diseases together.

Getting drugs where they are most needed is the greatest challenge, says William Lin of Johnson & Johnson. Lin is in charge of his company's effort to donate 50 million doses of mebendazole, used to treat hookworm and other helminths. "I've asked them to ramp up production," he says. "I don't want to be left at the end of the year with stores in the warehouse—and egg on my face." **–GRETCHEN VOGEL**

BIOMEDICAL RESEARCH POLICY

NIH Lends a Hand to Postdocs Seeking to Become Independent Researchers

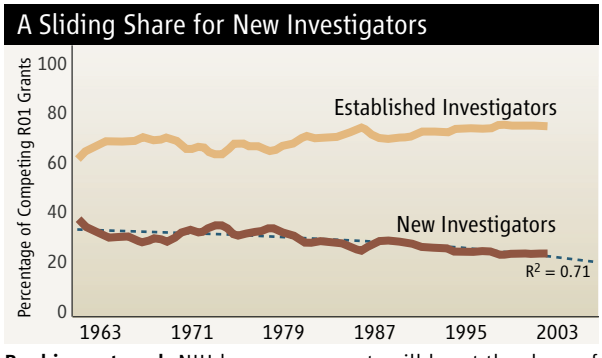
Concerned about the graying of the investigators it funds, the National Institutes of Health (NIH) last week unveiled a new "bridge" grant to help postdocs become independent researchers. Individuals could receive nearly $1 million over 5 years to cover research and training expenses. The first awards will be made next fall.

Even in tight budget times, "nothing is more important than supporting the new investigators early," said NIH Director Elias Zerhouni of the $390 million program. The funding will come from taking a "sliver" of each institute's overall budget, Zerhouni says. The chair of a 2005 National Academies panel that recommended the award's creation is delighted with the result. "This is exactly the sort of thing we were hoping for," says Thomas Cech, president of the Howard Hughes Medical Institute in Chevy Chase, Maryland.

The average age of a Ph.D. investigator winning his or her first research grant, called an R01, has risen from 37 to 42 in the past 25 years. Nearly a decade ago, NIH abandoned a smaller research award for young investigators because it didn't seem to help scientists get R01s. Now NIH is trying again.

The Pathway to Independence award combines traditional training and research grants (*Science*, 9 December 2005, p. 1601). The first 1 or 2 years cover the completion of a postdoc, at $90,000 per year (including 8% for overhead costs). Grantees who win a position as a tenure-track assistant professor can then apply for up to $250,000 a year for 3 more years for research. NIH says non–tenure track research faculty members are also eligible. The hope is that these investigators will then be in a good position to win R01s.

The research portion of the grant will cover full overhead costs, which can be as high as 50%. That feature should give universities a strong incentive to create positions for these investigators, Zerhouni says. "This is going to make it a lot easier for postdocs to get a faculty position because they're bringing so much money with them," adds Alyson Reed, executive director of the National Postdoctoral Association, which had also recommended the award's creation.



Bucking a trend. NIH hopes new grants will boost the share of competing research grants now going to new investigators.

SOURCE: NIH

NIH hopes to award 150 to 200 fellowships a year in the next 6 years to postdocs sponsored by their institutions. "That's enough to really make a difference," says Cech. Indeed, NIH hopes that the new award will help boost the share of R01s going to new investigators from 20% to 25% (see graph). Cech says it's also important that non-U.S. citizens are eligible and that the grants can be transferred to other institutions.

NIH is still weighing another recommendation from the academies panel for a new-investigators R01 program with grants based on experience rather than data. NIH's environmental health institute has begun a pilot project to test the idea.

YYePG Proudly Presents,Th→**JOCELYN KAISER**

Chinese HIV Offensive

BEIJING—Although China has fewer people with HIV than previously estimated, the health ministry is about to expand efforts to curb new infections.

Last week, the ministry and two U.N. bodies announced that China in 2005 had approximately 650,000 HIV carriers, including 75,000 AIDS patients. That's 190,000 fewer than in 2004, a decline largely attributed to better data collection. But the number of new infections is increasing, with 70,000 having contracted the virus last year. The ministry now plans to expand condom distribution and methadone and clean needle provision for heroin addicts. One high-risk group that will get extra help is China's 120 million migrant workers who travel from villages to cities, says ministry official Yao Deming. **–GONG YIDONG**

Biotech Knockoffs Hit Europe

LONDON—A synthetic human growth hormone called Omnitrope—a generic version of an out-of-patent drug by New York–based Pfizer called Genotropin—may soon be available in European pharmacies. It's expected to be the first so-called biosimilar drug to be marketed here or in North America and could lead to a flood of less costly biotech products. Pfizer had argued that regulators should be wary of approving any such biosimilar drugs because quality and safety depend on unique properties and exquisite control of batch processing. But a scientific panel of the European Medicines Agency gave the green light last week, and the European Commission will likely follow in 90 days.

The European vote raises the stakes at the U.S. Food and Drug Administration, which has been sitting on a similar appeal from Sandoz. **–ELIOT MARSHALL**

Clouds of Silence?

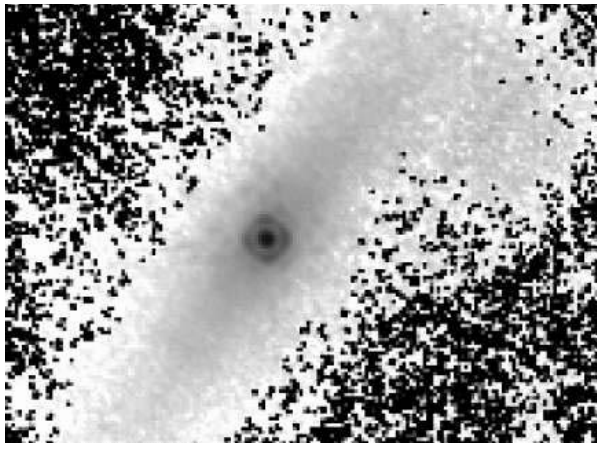
The chair of the House Science Committee has criticized NASA for what he sees as its heavy-handed treatment of James Hansen, director of NASA's Goddard Institute for Space Studies in New York City, a longtime voice on the dangers of global warming. "Good science cannot long persist in an atmosphere of intimidation," says Representative Sherwood Boehlert (R–NY) in a letter to NASA Administrator Michael Griffin sent this week after news reports that the agency is trying to muzzle Hansen. "NASA is clearly doing something wrong," wrote Boehlert. NASA officials insist that all agency employees are subject to the same rules, and that Hansen is not being singled out. **–ANDREW LAWLER**

THEORETICAL PHYSICS

Ring Around a Quasar May Deflate Quantum Foam After All

A halo in an image of a distant galaxy rules out some conceptions of the frothy "quantum foam" thought to make up space and time at the smallest scales, a team of physicists claims. If true, the observation clamps the first experimental limit on quantum gravity, the highly theoretical field that strives to marry quantum mechanics and Einstein's general theory of relativity.

Ironically, 3 years ago the team shot down a similar claim that quantum foam would obliterate the optical artifact. But the new analysis takes into account a physical effect the previous work missed, and others say it appears sound. "I looked at it as carefully as I could, and I could not find any obvious mistake," says Eric Perlman, an observational astrophysicist at the University of Maryland, Baltimore County.



Bubble burster. Irislike "Airy ring" around quasar PKS 1413+135 (black dot, *center*) may nix some versions of quantum foam.

The halo appears around a quasar—the fiery heart of a galaxy—in an infrared image the Hubble Space Telescope snapped in 1998. The "Airy ring" arises because light waves distort slightly as they bounce off the edges of a telescope's mirror, in ways that create rings around any pointlike object.

But the effect occurs only if the waves remain neat and orderly as they travel the 4 billion light-years from the quasar. Quantum foam would fuzz them out, say theoretical physicist Yee Jack Ng and colleagues at the University of North Carolina, Chapel Hill. So the halo rules out the most chaotic models of the foam, they argue in a paper to be published in *Physical Review Letters*. That's a big claim, as most theorists agree that the foam is an unavoidable consequence of melding quantum uncertainty with Einstein's notion that spacetime is stretchy and dynamic.

In 2003, astrophysicists Richard Lieu and Lloyd Hillman of the University of Alabama, Huntsville, also concluded that the halo torpedoed the notion of quantum foam. Within the minuscule foam, concepts of distance and duration lose precise meaning. As a result, Lieu and Hillman argued in the *Astrophysical Journal*, quantum foam should create an uncertainty in how far the light from the quasar had to travel to reach Hubble. That uncertainty should blur the wave fronts and eliminate the ring.

But Lieu and Hillman assumed that the uncertainty would grow in proportion to the distance to the quasar. Ng and colleagues pointed out in the *Astrophysical Journal* that if the foam varied randomly, then the uncertainty would increase in proportion to the square root of the distance, making the effect imperceptibly small.

Now, Ng and colleagues have considered uncertainties not only in the distance the light travels but also in its direction, which changes as the light scatters off the "bubbles" in the foam. The scattering greatly increases the blurring effect, Ng says. So the presence of the ring rules out a randomly varying quantum foam after all. Less random versions could still exist, however, as fluctuations in the foam might conspire to reduce the blurring.

"In my view, this is a compelling argument," says Demos Kazanas, a theoretical astrophysicist at NASA's Goddard Space Flight Center in Greenbelt, Maryland. Giovanni Amelino-Camelia, a quantum gravity theorist at the University of Rome "La Sapienza" in Italy, says, "I'm starting to believe that I should invest in this" line of inquiry.

As for Hillman, who died in 2005, and Lieu, "their suggestion was a good one, even if their argument was flawed," Ng says. Researchers can test the idea by looking for halos in images of other quasars, and larger telescopes should be able to detect smaller effects of the foam and probe other theoretical models.

–ADRIAN CHO

U.S. INNOVATION

Bandwagon Builds for Energy Research

Influential Washington policymakers have decided that bolstering U.S. technical know-how and tackling energy challenges should go hand in hand. Their solutions are featured in a series of recent legislative proposals, including the bipartisan Protecting America's Competitive Edge (PACE) package, introduced in the Senate last week. The more-than-$70-billion package, like several other bills introduced in December, includes more money for researchers and science educators funded by the Department of Energy (DOE).

The rapid economic development in India and China, a stagnant U.S. manufacturing base, and the poor performance by U.S. students on standardized tests in math and science have spurred a surfeit of recent legislative plans to tackle domestic competitiveness. Meanwhile, the rising demand for oil, tensions in the Middle East, and concerns about carbon emissions are pushing lawmakers to accelerate the development of new energy technologies. Both challenges were mentioned in a National Academies report released last fall (*Science*, 21 October 2005, p. 423). Previewing his State of the Union address earlier this week, President George W. Bush told Bob Schieffer of *CBS News* that an effort "to promote and actively advance new technologies" could make the U.S. "independent from foreign sources of oil."

Sunny and hot forecast. New funding proposals would boost energy research for areas such as photovoltaics and inherently safe nuclear power (shown here, a decommissioned plant in Hercules, California).

That rhetoric signals the demise of an era in which "congressional support of science was built on the pillars of defense and health," says former Massachusetts Institute of Technology president Charles Vest, who predicts that energy-environment, ▶

CREDITS (TOP TO BOTTOM): E. S. PERLMAN *ET AL.*, *ASTRONOMICAL JOURNAL* **124**, 2401 (2002); NREL

competitiveness-innovation, and health will be the new drivers of research funding.

Some would like to recreate the excitement of the Apollo space program in the 1960s by picking a challenging technological target that could weld research with national priorities. Norman Augustine, former chair and CEO of Lockheed Martin, chaired the academies' panel, which considered a so-called National Energy Initiative. Likewise, lawmakers crafting the PACE act at one point toyed with targeting development in specific energy areas such as nuclear energy. But the "decision was to let that happen [naturally]," says PACE co-sponsor Senator Pete Domenici (R–NM).

That approach is fine with Augustine. A focus on energy "happens to coincide with physics, engineering, and math," he says. Both PACE and the academies report also call for a 10%-a-year boost in federal funding for basic research.

PACE would give DOE an increased role in encouraging college students to major in science and engineering and improving training for science and math teachers at all levels through new scholarships. It also calls on DOE's national laboratories to support summer internship programs for gifted students. Insiders say Raymond Orbach, head of DOE's Office of Science and a former university president, helped persuade lawmakers to give DOE a larger national role in science education.

One proposal in several of the bills is a new DOE research agency modeled on the Pentagon's Defense Advanced Research Projects Agency. Aimed at encouraging risky, high-payoff energy science, the new agency, dubbed ARPA-E, would recruit academic and industrial leaders for short periods to craft and manage innovative research initiatives. Nobelist Steve Chu, director of DOE's Lawrence Berkeley National Laboratory in California, says that such an agency would help "bridge the funding gap" that now exists between well-established yet risky science, such as fusion research, and basic work with hard-to-anticipate benefits, such as that in particle physics. ARPA-E is also part of a package of bills introduced in December by Representative Bart Gordon (D–TN), ranking Democrat on the House Science Committee, and a recent proposal by Senate Democrats. Although not mentioned by name, the approach is also endorsed in a December innovation bill introduced by Senators John Ensign (R–NV) and Joe Lieberman (D–CT).

These legislative proposals may reflect a convergence of thinking in Congress. But supporters will also need to convince spending panels. Advocates don't see that as an insurmountable obstacle. PACE co-sponsor Senator Lamar Alexander (R–TN), for example, calls PACE's multibillion-dollar cost "a small price for a high standard of living."

–ELI KINTISCH

CREDIT: D. NORMILE

SCIENTIFIC CONDUCT

Panel Discredits Findings of Tokyo University Team

TOKYO—A University of Tokyo chemist has been stripped of his teaching duties and his graduate students following an investigation unprecedented in Japanese academia. Last week, university officials announced that a group led by Kazunari Taira has been unable to reproduce findings from four key papers. Taira maintains he has done nothing wrong aside from failing to ensure that experimental data were properly recorded. The headline-grabbing case is likely to spur other institutions to establish procedures for handling misconduct allegations.

Case closed? A University of Tokyo panel has concluded that certain findings from chemist Kazunari Taira's team could not be substantiated.

An investigation began last spring after the RNA Society of Japan wrote to the university raising questions about 11 papers that appeared between 1998 and 2004 in *Nature*, *Nature Biotechnology*, the *Proceedings of the National Academy of Sciences*, and other journals. The society acted on reports from scientists in Japan and from overseas saying they could not replicate the group's results, sources say. Hiroaki Kawasaki, a research associate in Taira's lab, was first author on 10 of the 11 papers. Taira was corresponding author of nine papers; he and Kawasaki were co-authors of the other two.

A panel led by Yoichiro Matsumoto, a mechanical engineer in the Graduate School of Engineering, was formed to probe the RNA Society's concerns. In an interim report released last September, the committee announced that a number of specialists contacted by the panel claimed they were unable to reproduce [illegible] the committee then selected four papers for a closer look and found that the group could not produce raw data or notebooks to support the findings (*Science*, 23 September 2005, p. 1973).

Taira insisted that he could repeat the experiments, so the committee asked him to do so. Kawasaki claimed to have replicated the findings in one of the papers, but the panel found that he had used materials different from those described in the original paper. Taira says more time is needed to work on the other experiments. However, at a 27 January media briefing, Matsumoto said bluntly, "At this time, there is no evidence the experiments can be repeated."

Junichi Hamada, a university vice president, said at the press briefing that both Taira and Kawasaki will now face a disciplinary committee and could be dismissed. In the meantime, the Graduate School of Engineering has relieved Taira of teaching duties and transferred his 25 graduate students to other teams. His own research has ground to a halt, and he says he will have to restart his career "from scratch."

"If I was just making up data, I wouldn't have had to work the 100 hours a week I was working," says Taira, whose recent studies involve RNA. But he concedes that his group is having trouble reproducing some results.

The investigation was the first ever by the University of Tokyo, widely considered to be Japan's most prestigious. The university is mulling the establishment of a permanent committee or office to address research misconduct, says panel chair Matsumoto.

Observers say they are pleased with the outcome. "The University of Tokyo should be highly praised for its handling of this investigation," says Norihiro Okada, a molecular biologist at the Tokyo Institute of Technology and one of the members of the RNA Society who urged an inquiry.

Okada and others believe that the case has focused attention on the need for more policing of misconduct. RIKEN, the nation's premier collection of basic research institutes, is ahead of the game. Its auditing and compliance office, created last April, now has the authority to investigate any hints of misconduct. Each RIKEN group must now make experimental records available for inspection for 5 years after publication, and the contributions and responsibilities of every author must be made clear. Office director Fumikazu Kabe says the policy might have to be modified for adoption by universities, "but it probably is something they could use as an example."

–DENNIS NORMILE

Neuroscientists have recently shown that multiple brain regions are used to judge short intervals, but fierce disagreement continues over how neurons in those regions measure time

A Timely Debate About the Brain

ANY DRIVER WILL AGREE THAT A YELLOW light at a traffic intersection presents a conundrum. Should one hit the brakes to stop or keep going—speeding, if necessary, to beat the red light? A number of factors could influence the choice, including the degree of recklessness of the driver, the urgency of the trip, and, not least, whether a police car is in sight. But the key element in the decision is the person's estimate of how much time it will take for the signal to turn red.

Time is integral to myriad other questions in everyday life: how long to grill one side of a burger before flipping it, how long to let a phone ring before hanging up, or how long to wait during a pause in conversation before treating it as a speaking cue. In both people and animals, the brain's ability to keep track of intervals is fundamental to innumerable behaviors. Some, such as walking and singing, rely on timing on the order of tens to hundreds of milliseconds. Others, such as foraging and making decisions, including the yellow-light problem, involve judgment of intervals on the scale of seconds to minutes and hours. As Warren Meck, a cognitive neuroscientist at Duke University in Durham, North Carolina, puts it: "Timing is everything."

For decades, researchers have sought to uncover the neural basis of time perception. They've been motivated in part by success at understanding the circadian clock: the biological timer that regulates the day-night cycle. In mammals, this 24-hour timepiece has a specific home: the brain's hypothalamus. Not surprisingly, scientists have hoped to discover a localized structure somewhere in the brain dedicated to tracking shorter time intervals. But now, timing researchers are all but abandoning the search for such an interval timer in any single region of the brain. Instead, they are increasingly convinced that the brain judges intervals on short time scales—milliseconds to minutes and hours—with the help of a distributed network of neurons. This shift is being driven by a slew of findings from electrophysiological studies on animals, behavioral experiments involving patients with brain lesions, and neuroimaging studies of healthy people.

> **"We're finally getting some neural reality** into the picture."
>
> —Russell Church, Brown University

In addition to identifying the different brain regions that play a role in timing, these experiments are prompting scientists to reexamine the classic view of how neurons keep track of time. And even though that has not yet led to a mechanistic account that satisfies everybody, researchers say the effort is helping to take timing research beyond the speculative realm of psychology into the firmer territory of neuroscience. "We're finally getting some neural reality into the picture," says Russell Church, a psychologist at Brown University, who has studied timing for more than 40 years.

A distributed timekeeper

Inspired by the hypothalamic circadian clock, researchers began looking for a short-time-scale clock in the brain in the 1970s. Some focused on the hippocampus, assuming that time perception was related to memory. Others searched the cerebellum. By the mid-1990s, many were convinced that the clock was located in the basal ganglia.

Yet in recent years, neuroscientists have linked multiple areas throughout the cortex to time perception. Some evidence has come from neuronal recordings in animal brains. In 2003, for example, Michael Shadlen, a neuroscientist at the University of Washington, Seattle, and his graduate student Matthew Leon reported training monkeys to make eye movements based on duration judgments in the range of 0.3 to 1 second. The two found that neurons in the animals' posterior parietal cortex increased their firing rate based on how much time had elapsed. The results suggested that these neurons track the flow of time relative to a remembered duration. Other teams of researchers, including one led by Yoshio Sakurai of Kyoto University in Japan, and a group led by Carlos Brody at Cold Spring Harbor Laboratory in New York, have observed similar patterns of neuronal activity in the prefrontal cortex of monkeys performing timing tasks.

Evidence for the involvement of different cortical areas in timing has also come from

CREDIT: GETTY IMAGES

studies of patients with brain lesions. In 2002, a team led by Giacomo Koch, then at Italy's University of Rome, reported on a patient with a prefrontal cortical lesion who underestimated durations of a few seconds—time to him seemed to pass more quickly than it actually did. The same year, a group led by Marc Wittmann of Ludwig Maximilians University in Munich, Germany, described patients with lesions in other cortical areas who also underestimated durations longer than 3.5 seconds. Then in 2003, Koch and his colleagues showed that they could induce healthy subjects to underestimate multisecond intervals by suppressing their prefrontal cortices with a focused magnetic field.

Some of the clearest evidence for a distributed picture of timing has come from neuroimaging studies. In one such study, researchers in France asked 12 subjects to compare the color and duration of two circles presented one after the other on a computer screen (*Science*, 5 March 2004, p. 1506). Each circle was colored one of three shades of purple and stayed on for one of three durations: 0.5, 1, or 1.6 seconds. In some trials, the subjects had to indicate if the second circle was bluer or redder than the first; in others they judged if the second circle appeared for a longer or shorter duration.

Functional magnetic resonance imaging scans of the volunteers showed activation of an extensive network of brain areas during the time estimation task; in contrast, only the V4 area of the visual cortex lit up during the color-judgment task. Also, the various areas that lit up during the timing task—including the prefrontal and parietal cortices and the basal ganglia—showed increases in activity as the subjects paid more attention to time.

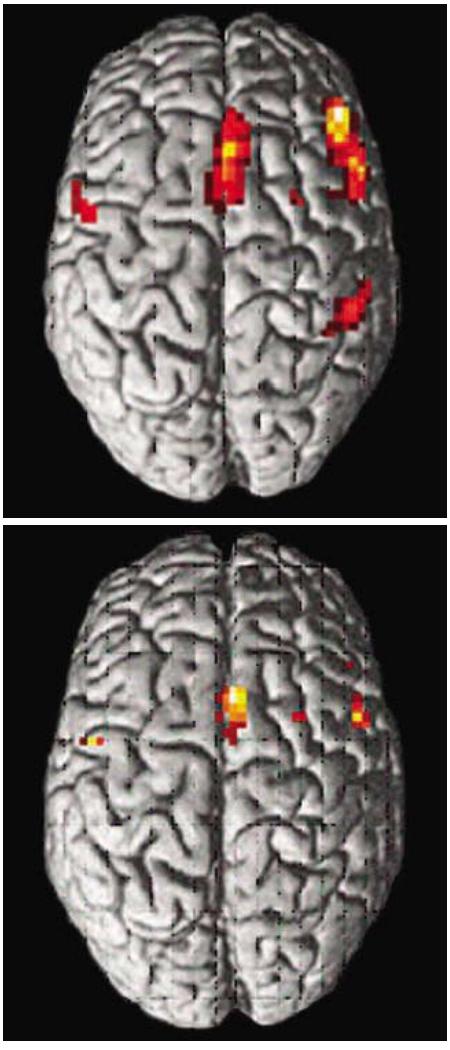
"Although visual features such as color or motion or form can be linked to single-feature-specific processing areas, timing information appears to be coded in a distributed network of brain regions," says Jennifer Coull, a cognitive neuroscientist at the Centre National de la Recherche Scientifique in Marseille, France, and lead author of the study. "Maybe we have to integrate several sources of information in order to estimate time because it is so much less tangible to our senses than visual features."

In the August issue of *Human Brain Mapping*, a different French group led by Viviane Pouthas of the Salpêtrière Hospital in Paris reported activation in a similar set of brain regions when subjects timed intervals that were about 0.5 and 1.5 seconds long. The researchers also observed that a subset of these regions—including certain areas of the cortex and the striatum—showed higher activity when subjects estimated the longer duration. Pouthas says this subset could be playing a direct role in time estimation, distinct from other components of the task such as recalling and comparing intervals.

CREDIT: V. POUTHAS/HOPITAL DE LA SALPETRIERE

How it works: The old and the new

Although most researchers are now convinced that timing involves multiple regions of the brain, they disagree on how neurons actually keep track of time. Until recently, the prevailing theory had been that some neurons release pulses of one or more neurotransmitters at periodic intervals while other neurons accumulate them, in the same way that a cup placed under a steadily dripping faucet accumulates drops of water. As the receiving neurons register more and more signals, the sense of time that has passed grows. Moreover, quantities of accumulated pulses corresponding to specific durations are recorded in long-term memory, allowing an individual to compare newly encountered time intervals to those previously experienced.



Spread out. Multiple brain regions are activated in a time-estimation task (*top*); a few of these regions (*bottom*) show increased activation while estimating longer intervals.

This account of time perception—known as the pacemaker-accumulator model—has held sway since it was proposed in the 1970s by the late John Gibbon, a psychologist at Columbia University. Researchers have found the model to be a handy framework for explaining a fundamental feature of timing, seen in both animals and humans, called the scalar property—which is that the amount of error in estimating time intervals increases linearly with the duration being timed. The model has also provided psychologists with a good handle on a variety of other behavioral findings related to timing.

But now it is being challenged by some as too simplistic—and perhaps even fundamentally flawed. One challenger is Meck, a protégé of Gibbon and once a strong proponent of the pacemaker model. His group has recently put forth a new idea that has garnered support from many in the field but strong criticism from others.

Meck spent the 1980s and the early 1990s seeking to identify the neural pieces of the pacemaker-accumulator model. Although this system could in theory operate in a specific brain region, it could also involve multiple regions, as might be expected by the more recently embraced idea of a distributed neural network. Working with Chara Malapani, a clinical psychiatrist at the New York Psychiatric Institute in New York City, and others, Meck proposed in the mid-1990s that the brain's stopwatch was located in the basal ganglia, comprising dopamine-secreting "pacemaker" neurons in the substantia nigra and "accumulator" neurons in the striatum. Some of the evidence for this hypothesis came from studies of Parkinson's disease patients, whose poor performance on timing tasks was found to be linked to the loss of dopamine-producing neurons. Researchers found that medicating these patients with L-DOPA, a drug that increases dopamine levels, improved their timing.

Even though the dopamine work seemed to put flesh on the pacemaker theory, the model ran into trouble a few years later. At the time, Meck was already somewhat skeptical about the capacity of neurons to linearly sum up temporal pulses over the course of seconds to minutes. Then one of his doctoral students, Matthew Matell, marshaled evidence from the neurobiological literature that convinced Meck that dopamine could not drive neurons in the striatum to fire in the simplistic way proposed by the pacemaker model.

Meck and Matell have developed an alternative model in which the striatum reads out intervals from a snapshot of activity across a network of cortical neurons. The different neural populations in the cortex—all connected to neurons in the striatum—have firing rates that oscillate at different frequencies. At any given point, the pattern of activity across the cortical network—the synchronous firing by a certain ensemble of

neurons—represents the brain's temporal signal, a distributed code that Matell calls the "clock input."

When an event has to be timed, the cortical clock is reset through a synchronization of neuronal firing in the network. The neurons in the striatum track the evolving network's activity, until some kind of reinforcement arrives, marking the end of the timed interval: a pellet of food for a rat in a timing experiment, or the change of light for a driver at a traffic intersection. Each reinforcement triggers the substantia nigra to release a wave of dopamine onto striatal neurons, helping to establish a link between their firing and the pattern of activity in the network at that moment. After a number of experiences with a given duration, the striatal neurons start to recognize the snapshot of coincident activity at the moment of reinforcement and are driven to intensify their firing at that moment, indicating that the timed interval is up. This snapshot is filed away in memory for future reference, although Meck and Matell's model doesn't fully explain how this is done.

"You could imagine the cortical network as a symphony playing a concerto, while the striatum acts as a listener," says Matell. "When the musical piece comes to a point where the violins and the flutes and the tympani all cooccur—that is, when a particular ensemble pattern of neurons is simultaneously active—the listener decides that a particular duration has elapsed. One could take this analogy further and propose that attention or consciousness serves as the conductor of the symphony."

The new model, which Meck and Matell have named the striatal beat frequency (SBF) model, represents a dramatic shift from the pacemaker model because it fundamentally rejects the intuitive notion of time flowing like sand in an hourglass, collecting in a heap as the moments pass. Not only does the new model predict the scalar property of timing, say the two researchers, it is supported by neurophysiological findings. In experiments in which rats were trained to estimate a 40-second duration, Meck, Matell, and a colleague found that the firing rate of striatal neurons peaked at the end of the trained interval, as predicted by the SBF model. Meck and Matell say the recent studies pointing to a distributed picture of timing buttress their theory.

The SBF model "elegantly allows for the timing of multiple intervals and higher-order temporal structure," says Dean Buonomano, a cognitive neuroscientist at the University of California, Los Angeles. "But more importantly, it eliminates the need of an accumulator circuit, for which there is little support that comes as naturally to neurons as does coincidence detection."

Not everybody has been as kind. "Pure fantasy" is how Shadlen describes the model. "Synchronous spikes are ubiquitous in the cortex; there are thousands of neurons firing simultaneously at any given time," he says, arguing that it's unrealistic to think that such widespread patterns might serve as distinct temporal codes. Shadlen contends that it's more likely that "time is wrapped up inextricably with expectation" and is represented as part of an anticipatory buildup signal (in line with the pacemaker idea) in each of the cortical areas that might be involved in carrying out a task. As evidence, Shadlen points to work that he and a colleague reported in *Nature Neuroscience* last year in which they recorded such ramplike activity from neurons in the posterior parietal cortices of monkeys that performed eye movements based on time estimates.

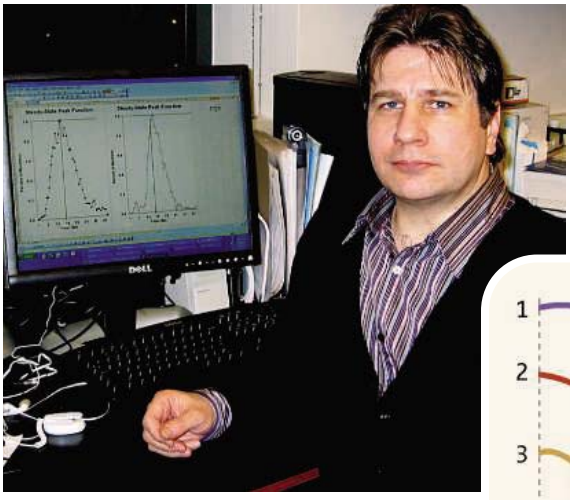
The precise pattern of coincident activity in the cortex changes over time and could thus serve as a duration code, responds Matell. "Using the symphony analogy, there are many musicians playing pretty much throughout a piece of music. And yet, the piece of music is distinguishable at one point in the piece from another point in the piece." Matell adds that the neurons recorded in Shadlen's monkey experiments could be firing in response to a temporal readout provided by the striatum rather than representing time themselves.

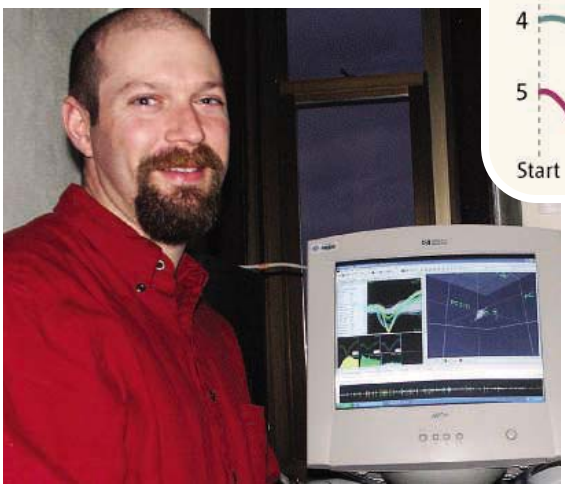
John Wearden, a psychologist at Keele University in the U.K., levels another charge against the SBF model and similar ideas sometimes grouped as nonclock models. Because different times in the SBF model are represented as different patterns of neuronal activity, he says, there's no way to tell if one interval is longer than another, even though that's something people naturally judge all the time.

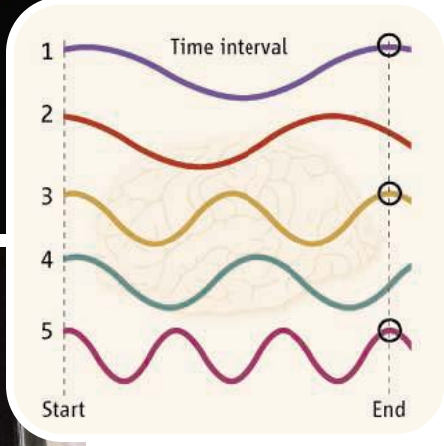
The SBF model permits such comparisons, counters Matell: "If you provided me with two durations, I could time the first duration—let's say that's the longer one—learn its cortical snapshot, and then evaluate whether the second cue finished before my 'time's up' for the first or vice versa," he says.

Trying to address some of the field's skepticism, Meck and Matell are looking to refine and test their model by recording neurons from multiple sites in rat brains, and by electrophysiological and neuroimaging studies of Parkinson's disease patients. Regardless of whether the SBF model survives, they and many others feel there's little chance of returning to the classic view of a discrete hourglass in a single brain region. As Buonomano puts it, "The notion that timing relies on a centralized single pacemaker-accumulator is on its deathbed."

–YUDHIJIT BHATTACHARJEE







The right moment. Warren Meck (*top*) and Matthew Matell (*bottom*) propose that striatal neurons recognize a learned interval from detecting the pattern of coincident activity across different neural populations. The input from populations that are active at that instant (1, 3, and 5) cause the striatal neurons to step up their firing rate, marking an interval's end.

CREDITS (TOP TO BOTTOM): COURTESY OF W. MECK; COURTESY OF M. MATELL; K. BUCKHEIT/*SCIENCE* (INSET)

CREDIT: KEVIN WOLF/ASSOCIATED PRESS

PROFILE: ARATA KOCHI

Fighting Words From WHO's New Malaria Chief

Just months into his new job, Arata Kochi is battling big pharma on drug resistance

A new heavyweight champion has stepped into the ring to fight the global scourge of malaria. Less than 3 months after taking office as director of the World Health Organization's (WHO's) malaria program, Arata Kochi wants the world to know that he's ready to rumble. At a 19 January press conference at WHO headquarters in Geneva, Switzerland, Kochi issued a 3-month ultimatum to the global pharmaceutical industry to stop selling the single-dose form of the drug artemisinin because of the danger of creating resistant strains of the malaria-causing parasite. Kochi threatened to name and shame 18 offending drug companies and said his next step would be to lobby for a "complete ban" of those companies' other malaria medications. "The quiet approach will never work," Kochi told *Science*.

The announcement is a departure for WHO, an international organization that usually relies on consensus before taking action. "We have often been criticized for being slow and ineffective," says Pascal Ringwald, a medical officer in WHO's Roll Back Malaria program. "But if resistance [to artemisinin] appears tomorrow, the WHO cannot be blamed for saying nothing."

First extracted from the common wormwood shrub by Chinese scientists in 1972, artemisinin is the most effective drug today against malaria, with a single dose curing 90% of cases within days. Because resistance to the other malaria drugs is on the rise everywhere, artemisinin is seen as the last defense against a disease that kills 1 million people each year, most of them African children. Initially, scientists thought it unlikely that the parasite could develop resistance to artemisinin because of its mode of action—a peroxide group that releases destructive oxygen atoms. But both the exact mode of action and the possibility of resistance are still in doubt, and experts are alarmed at the recent discovery of a mutation in the parasite that reduces its sensitivity to the drug (*Science*, 9 December 2005, p. 1607).

Although no one has yet died of artemisinin-resistant malaria, says Ringwald, "the warning signs are all there." To prevent resistance, scientists and WHO officials have been urging governments for the past several years to use artemisinin only in cocktails of multiple drugs called artemisinin-based combination therapy (ACT). "If we lose artemisinin, we lose ACT, and it could be 10 years before a new drug is available, which would be a catastrophe," says Ringwald.

Kochi may be a newcomer to the malaria scene, but he's no neophyte to global health. A Japanese public health physician trained at Harvard University, he directed WHO's tuberculosis (TB) programs for 10 years, turning a fledgling two-member staff into one of its flagship programs. "Kochi had a vision" for how to combat TB, says Nils Billo, director of the Paris-based Union, the main fight against Tuberculosis and Lung Disease, "which now most of the countries of the world have adopted and implemented." Despite his efforts, however, TB remains a major threat—an appeal for a fresh attack on TB was launched last week in Davos, Switzerland.

With Kochi now focused on malaria, his bold opening move is yielding mixed reviews. "The need to switch from monotherapy to ACT was recognized years ago," says Brian Greenwood, director of the London School of Hygiene and Tropical Medicine. "But antagonizing big pharma is not a sensible strategy." Greenwood argues that there is little money to be made developing and selling drugs for a disease that is nearly exclusive to the developing world and that "these companies are really only doing this for good public relations. We need their help if we're going to get medicines into poor communities." An official at one of the biggest companies on Kochi's list, Paris-based Sanofi-Aventis, told *Science* they plan to comply but added: "It is the responsibility of local authorities to implement the switch to ACTs, which is more complex and requires education."

Others involved with global health praise Kochi for "taking a stand and saying something that we've all been thinking," says Chris Hentschel, CEO of the Geneva-based Medicines for Malaria Venture. "We're behind him." Hentschel says that not all companies are making malaria medicines "just for charity" and that in some cases "they have been unhelpful."

Right or wrong, Kochi faces an uphill battle. "WHO has no powers to enforce and a very small budget," says Hentschel, "so the most it can do is damage a company's reputation." He predicts that smaller companies may ignore the ultimatum "because they feel they don't have any reputation to lose." One way WHO could make an impact, he says, would be to influence the decisions of big drug purchasers such as the U.N.'s children's fund UNICEF or the Global Alliance for Vaccines and Immunization.

> **"Antagonizing big pharma** is not a sensible strategy."
>
> —Brian Greenwood, LSHTM

For his part, Kochi seems confident. "When I named countries that weren't doing enough to fight TB in 1996, they responded and improved," he says. As proof that his strategy is sound, he notes that two companies on his list of 18—Switzerland-based Mepha and "a generic drug company"—have already promised to comply.

Kochi says his next targets are "gaps" in malaria research. "Malaria epidemiology is very weak," he says, "and we also need more consensus on how to diagnose the disease." Without "better science," Kochi says, strategies to combat malaria "will continue to be like religion, based on faith."

–JOHN BOHANNON

John Bohannon is a writer in Berlin, Germany.

Spending Itself Out of Existence, Whitaker Brings a Field to Life

The Whitaker Foundation took on the job of turning a fledgling field into a scientific heavyweight—and succeeded. But what happens to biomedical engineering now?

Bioengineer Sangeeta Bhatia and the Whitaker Foundation are scientific soul mates. As a graduate student in a joint M.D.-Ph.D. program at the Massachusetts Institute of Technology (MIT) and Harvard University in the 1990s, Bhatia attended the Whitaker College of Health Sciences and Technology, an interdisciplinary program for scientists and engineers in the Boston area that the foundation began funding in 1979. After graduation, Bhatia received a Whitaker young investigator's grant to set up her lab at the University of California, San Diego (UCSD), a school that has received $23 million from the foundation to build up its biomedical engineering department.

"The Whitaker award allowed me to get my very first piece of equipment and hire a graduate student," says Bhatia, now an associate professor at MIT. "It helped me launch my entire research program."

There and back again. Thanks to Whitaker funding, Sangeeta Bhatia has returned to MIT as an associate professor.

With grants from the National Institutes of Health (NIH) and the National Science Foundation (NSF), Bhatia appears well along the road to a successful academic career. And that's fortunate, as Whitaker is on the road to oblivion. In June, the foundation will shut its doors after 30 years and more than $800 million in scientific philanthropy. During its lifetime, the Arlington, Virginia–based foundation has invested in thousands of young faculty members and graduate students and built hundreds of laboratories. That investment has transformed biomedical engineering from a barely recognized discipline into one of the most popular science majors in the United States.

"Their impact is almost immeasurable," says Frank Yin, president of the Biomedical Engineering Society and chair of the biomedical engineering department at Washington University in St. Louis, Missouri. "Whitaker put biomedical engineering on the map."

As remarkable as its largess is the way Whitaker spent it. "Most foundations focus on a problem—such as world hunger—and anyone who has a tool to address this problem qualifies for funding," says Thomas Skalak, chair of the biomedical engineering department at the University of Virginia (UVA) in Charlottesville. "Whitaker was unique in that it tried to establish the permanence of a particular field. And it knew that to do this, it would need to build up the field's infrastructure." That thrust benefited young and promising scientists such as Bhatia, whom the foundation regarded as the future of the discipline.

But will biomedical engineering continue to thrive when Whitaker leaves the scene? Some fear programs that have just begun to blossom under Whitaker's care may wilt. Others are concerned that some young faculty members could be orphaned without Whitaker's support, stunting the entire field. And still others worry that the foundation may have overbuilt the field's academic structure, creating more departments than the discipline can maintain. "The changes over the next few years could be pretty dramatic," Yin predicts.

Going for broke

The Whitaker Foundation was never supposed to last forever. Its founder, U. A. Whitaker—an engineer and CEO of a company that manufactured textiles, tires, and shoes—set the foundation would fold within 40 years of his death in 1975. "He hated bureaucracy," says Whitaker President Peter Katona. "He felt that a foundation wouldn't accomplish its mission if it went after that mission forever."

Despite those concerns, Whitaker operated much like any other charitable organization in its early years. It spent about 10% of its capital annually (about $14 million) fostering collaborations between biologists and engineers to develop medical devices. Most of the money was channeled into 3-to-4-year grants to new faculty members such as Bhatia.

Like most biomedical engineers, Bhatia avoided a lengthy postdoc and moved directly into an assistant professorship. But there was a tradeoff: The quick transition prevented her from gathering enough research data to feel comfortable submitting a grant proposal to NIH. Another handicap was the project itself: designing a cartridge filled with liver cells that would help filter blood in patients with kidney failure. Its large engineering component, she felt, meant it "would never fly at the NIH." But once Bhatia had received the Whitaker award, she had the wherewithal to pitch a successful application first to NIH and later to NSF.

Although Whitaker's board was happy with the return on modest investments such as this, in 1991 it decided to go for broke. "The governing board wanted to increase the impact of the foundation when the field was at the cusp of becoming mainstream," says Katona. "They knew the only way to do this was to spend big bucks."

Ironically, exhausting the $200 million endowment proved harder than expected. Over the next 4 years, the foundation's assets more than doubled, thanks to the stock market boom. By the end of the decade, its annual payout of more than $60 million matched that of charities with an endowment of $1.2 billion.

One goal was to create thriving bioengineering departments at top U.S. universities. That's what happened at UCSD, whose program in 1988 consisted of six faculty members on half a floor of a medical school building. In 1993, Whitaker awarded the university $5 million to hire more professors and develop core facilities. Four years later, the foundation gave UCSD $18 million for a bioengineering building.

"The building brought together faculty and staff for the first time and really transformed the university into a national powerhouse for bioengineering," says Bhatia, who was hired under the first award. Today, UCSD has an official bioengineering department with 18 faculty members, 150 graduate students, and 1000 undergraduate majors—triple the pre-Whitaker numbers. *U.S. News & World Report* ranks the department second in the nation; before Whitaker, it wasn't even on the radar.

CREDIT: MARIO CASAL/HST

Dozens of schools can tell similar stories. Since 1991, the number of biomedical engineering departments in the United States has soared from 27 to 74, with accompanying increases in the number of undergraduates and graduate students.

Whitaker's smaller awards have made a big difference as well, says Skalak. At UVA, two $1 million awards allowed his department to create new biomedical engineering courses and establish dedicated lecture halls. Bhatia used similar awards at UCSD to write the first undergraduate textbook on tissue engineering and to help develop a Web site that allows all UC students to take biomedical engineering classes online. "Whitaker realized that these tools would help grow biomedical engineering as a discipline and were vital to the field's future," she says.

Engineering change

With Whitaker folding its tent, biomedical engineers are wondering if the field can continue to thrive. "There's a lot of trepidation in the field about what will happen now," says Bhatia. Thanks to the foundation's emphasis on infrastructure, the number of biomedical engineers continues to increase, even as funding remains static. But the field will also need to cope with the decline in start-up funding for new biomedical engineering faculty members, a $275 million program that over the past 15 years has given out 80 to 100 awards annually. "The loss of these awards is going to make it difficult for new professors," admits Katona, who says he'd much rather be entering the field 3 to 4 years ago than today.

The Miami, Florida–based Wallace H. Coulter Foundation offers early career awards in bioengineering, but they provide less money and last only 2 years. A better candidate to fill Whitaker's shoes is the 5-year-old, $300-million-a-year National Institute of Biomedical Imaging and Bioengineering (NIBIB). Aware of the needs of new investigators, NIBIB gives their grant applications a 5% bonus in merit reviews. "The idea is to cut new professors extra slack so they'll have an easier time getting funded," says Deputy Director Belinda Seto.

Thanks to the policy, Seto says seven additional biomedical engineering faculty members qualified for basic R01 grants last year, bringing the total to 24. In addition, she says young investigators can apply for exploratory R21 grants, which don't require preliminary research data and confer an average of $350,000 for 2 years. In 2005, 39 of these awards went to new faculty members.

Robert Nerem, director of the Parker H. Petit Institute for Bioengineering and Bioscience at the Georgia Institute of Technology in Atlanta, worries that such policies won't be enough. The R21s are too short, he says, and both he and Yin say that most of NIBIB's funding goes toward clinical imaging research rather than biomedical engineering. In addition, Nerem notes that NIBIB has one of the lowest applicant success rates at NIH. "So far, NIBIB has not stepped up to the plate," he says.

Another concern is that Whitaker may have overbuilt the field's academic structure, says Nerem. "Was building 60, 70, 80 departments really the right strategy?" he asks. The number of biomedical engineers graduating from many smaller schools may contribute to an oversupply in the short term, he says. That could eventually lead to a Darwinian crunch that hurts the smaller departments.

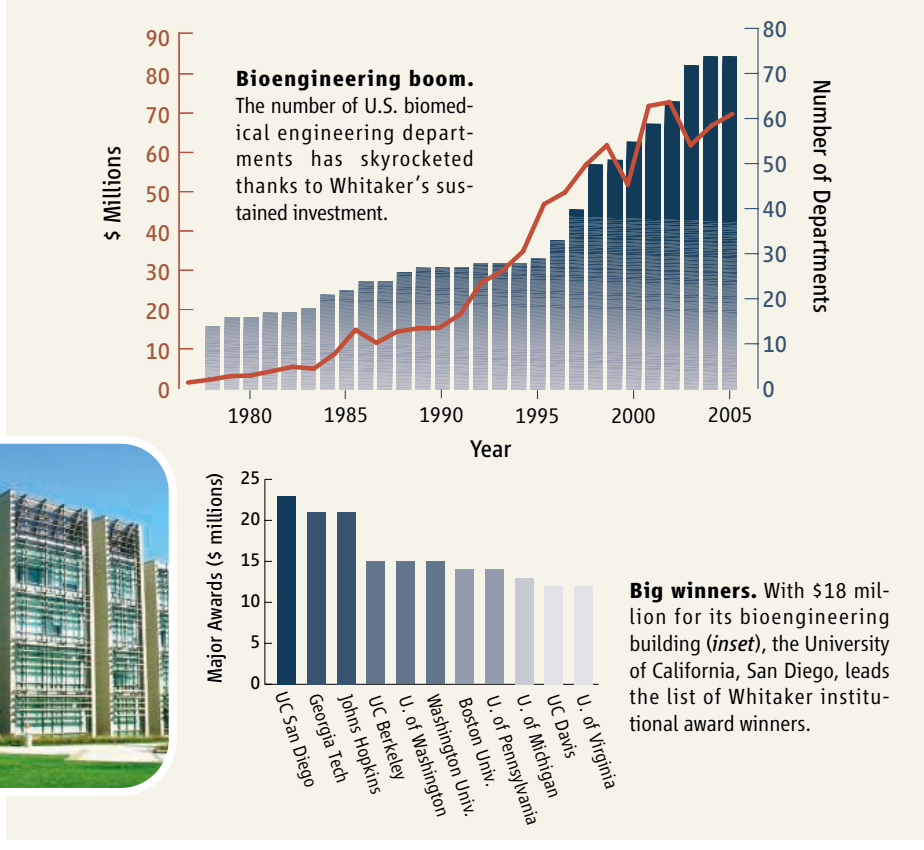
As the chair of one such department, Michael Neuman of Michigan Technological University in Houghton admits "Whitaker took a bit of a gamble with us" because of the school's isolated location on Michigan's upper peninsula, the lack of a nearby medical school, and its small life sciences program. To survive, Neuman says that programs such as his may have to change their focus from research to teaching, qualifying them for a larger university education department. For support

Yin expects other changes as well. As fewer faculty positions open up, graduates may find themselves doing longer postdocs, and more biomedical engineers may begin moving into new areas. Neuman has begun to see some of this already at Michigan Tech. A recent graduate joined the automotive industry and is studying the biomechanics of car accidents, he says. And a former student of Neuman's is a child abuse counselor who uses her education to assess, for example, whether a child really got his injuries from falling down a flight of stairs.

Although Whitaker may not have foreseen these changes, Katona, the foundation's president, is happy with the community's response. "I like the idea that some universities will do things differently and that not everyone is taking the same career path," he says. "We've done our job. … Now it's up to the field to have a midcourse correction if necessary."

Despite the challenges, Bhatia is optimistic that the interdisciplinary approach that permeates biomedical engineering and the growing demand for new medical technology will help sustain the field. Her new project uses nanoparticles to target drugs to tumors—the precise mixture of biology and engineering that Whitaker has tried so hard to foster. "Whitaker got us to this point by taking a risk," says Bhatia. "Now we must evolve without them."

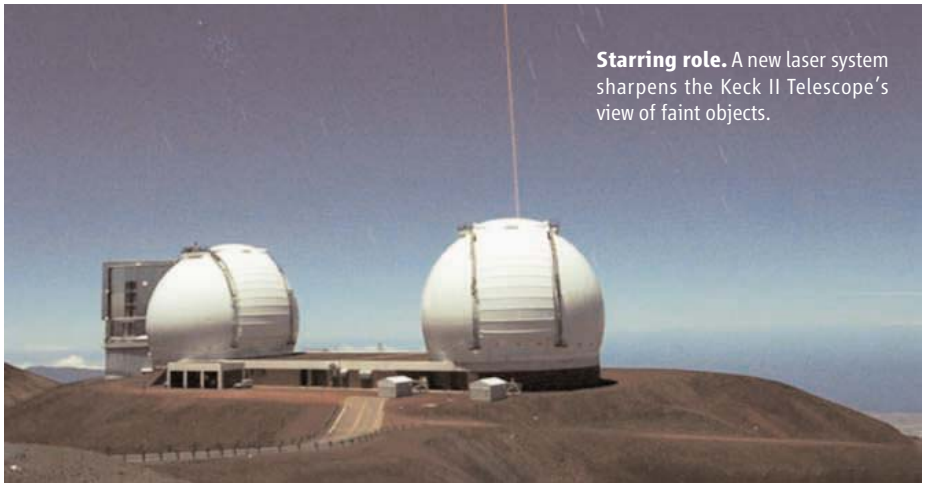
–DAVID GRIMM



Bioengineering boom. The number of U.S. biomedical engineering departments has skyrocketed thanks to Whitaker's sustained investment.

Big winners. With $18 million for its bioengineering building (*inset*), the University of California, San Diego, leads the list of Whitaker institutional award winners.

CREDITS: UNIVERSITY OF CALIFORNIA, SAN DIEGO (INSET); SOURCE: WHITAKER FOUNDATION



Starring role. A new laser system sharpens the Keck II Telescope's view of faint objects.

Laser Points to Bright New Era For Ground-Based Astronomy

Many dark nights at the W. M. Keck Observatory atop Mauna Kea, Hawaii, now feature a startling source of light: a laser beam emerging from one of the twin domes. Rather than swamping faint signals from the heavens, however, the photons have quite the opposite effect.

The long-awaited advance, called laser guide star adaptive optics, trumps the standard adaptive optics now used at most major telescopes. Light from a star jitters rapidly as it passes through Earth's shifting atmosphere. In the current systems, computers analyze that pattern, then flex a thin mirror within the telescope's optical path to correct the distortion. The result is steady vision rivaling that of the Hubble Space Telescope. But this technology requires light from a bright star or planet, limiting its application to about 1% of the sky.

In contrast, astronomers can aim the Keck laser nearly anywhere. The beam illuminates a layer of sodium atoms about 90 kilometers high, left there by incoming meteoroids. The flexible mirror sharpens the telescope's vision of this "star"—and, along with it, faint objects in the adjacent field of view. After years of tinkering, this system became available last year for routine scientific use on the 10-meter Keck II Telescope.

The first results delighted a packed session of observers at the meeting. "It's very clear that it has moved beyond an experimental development to mature science observations," says R. Mark Wagner, an instrument scientist for the Large Binocular Telescope at Mount Graham, Arizona. "They've made laser adaptive optics into a turnkey system," adds Jeremy Mould, director of the National Optical Astronomy Observatory in Tucson, Arizona. "You just use it to do astronomy, and you don't worry about whether it's going to work."

For example, astronomer Michael Liu of the University of Hawaii, Manoa, used laser-honed vision to study close pairs of the failed stars called brown dwarfs. Liu's team resolved one binary pair with distinct reddish and bluish colors, even though the dwarfs probably formed together in the same gaseous nursery. Liu believes the difference arises from the ebb and flow of iron-rich clouds in their gradually cooling atmospheres. "Binaries like this will be our Rosetta stones for understanding how clouds vanish at this critical transition," comments modeler Mark Marley of NASA's Ames Research Center in Mountain View, California.

In another laser-guided project, astronomer Judith Cohen of the California Institute of Technology in Pasadena short-circuited a dispute about tight clusters of stars orbiting the nearby Andromeda galaxy. Some researchers had claimed that a few of Andromeda's stellar clusters are as young as 1 billion years, even though all such clusters in our Milky Way are at least 9 billion years old. But with Keck's newly piercing view, Cohen found that most of the supposed clusters were much looser groupings of stars or even flaws in previous images.

Other targets have included satellites of bodies in our solar system's remote Kuiper belt; stars on swooping orbits around the ▶

Pulsar Sets a Dizzying Standard

Astronomers have broken a long-standing record by finding the fastest spinning object in space. The new champ is a neutron star—the ultradense remnant of a supernova explosion—rotating 716 times each second. If the star is about 20 kilometers wide, as assumed, its equator would whirl at 15% the speed of light.

The object is among dozens of newfound millisecond pulsars, so named for their clocklike pulses of radiation at hundreds of hertz (cycles per second). Astronomers led by Scott Ransom of the National Radio Astronomy Observatory (NRAO) in Charlottesville, Virginia, detected the pulsars in several of our galaxy's rich clusters of stars. Old pulsars in these tightly packed swarms get resuscitated when they interact with other stars and acquire binary partners. When such a companion star evolves into a bloated giant, intense gravity pulls its gas toward the pulsar. The infalling matter spirals onto the pulsar and whips up its spin. The previous standard-bearer of 642 hertz was the first millisecond pulsar found, in 1982. The long wait made some theorists doubt that the spin-up process could go much faster.

The new find explains part of the delay: The speediest millisecond pulsars appear screened by matter blasted off their companions, making them tough to spot. Graduate student Jason Hessels of McGill University in Montreal, Canada, and others worked with Ransom to tease out the pulsar's 716-hertz flashes, which vanish 40% of the time. An ongoing search of star clusters with a sensitive radio processor at NRAO's 100-meter Green Bank Telescope in West Virginia should unveil ever-faster spinners, Ransom says. The group reported its discovery at the meeting and in the 12 January online edition of ***Science*** (www.sciencemag.org/cgi/content/abstract/1123430).

In principle, pulsars could accelerate to 1500 to 2000 hertz before shattering from centrifugal force, says astrophysicist Deepto Chakrabarty of the Massachusetts Institute of Technology in Cambridge. "But it's quite striking that they are nowhere near that," he says. The new pulsar may have surpassed 1000 hertz at its peak. But Chakrabarty believes some physical mechanism—perhaps shedding of energy by gravitational waves—applied the brakes to the pulsar and its cousins soon after their rebirth.

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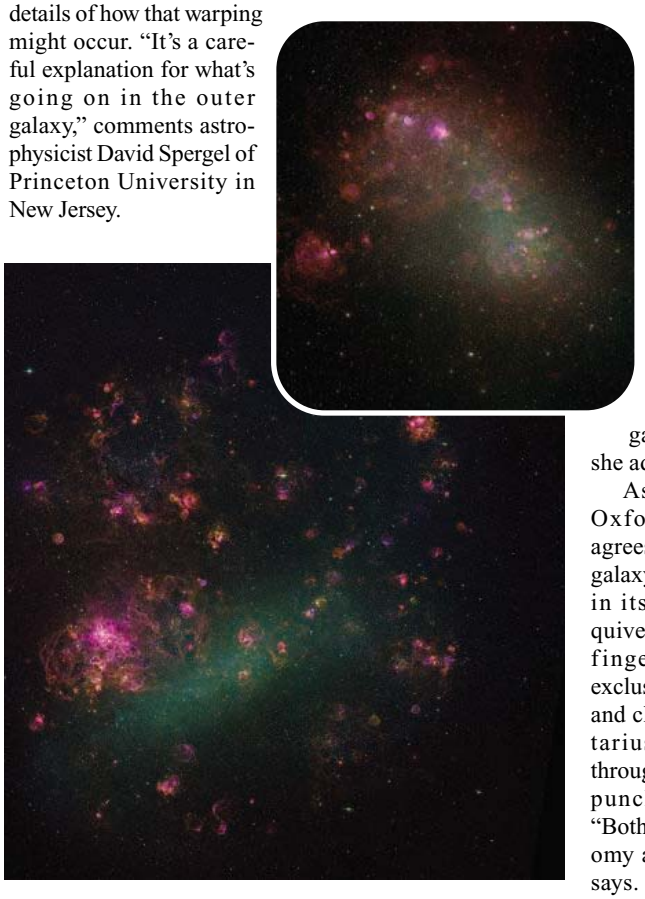
CREDIT: SARAH ANDERSON/W. M. KECK OBSERVATORY

black hole at the center of our galaxy; and the physical properties of galaxies where supernovae exploded more than 8 billion years ago. "These are the big leaps we were looking for," says Keck Director Frederic Chaffee.

Chaffee says Keck went to school on a prototype laser system at the University of California's Lick Observatory near San Jose. Several 8-meter telescopes are now catching up with planned laser-guided science runs later this year, including the U.S.-led Gemini North and Japan's Subaru Telescope at Mauna Kea, and the European Southern Observatory's Very Large Telescope at Cerro Paranal, Chile.

Pesky Companions Warp the Milky Way

Our galaxy wins no prize for symmetry. Its disk of gas and stars bends upward and downward, like the brim of a trampled hat. Astronomers have long suspected that dwarf galaxies orbiting the Milky Way perturb the disk, especially the Magellanic Clouds—two smudges of stars visible from the Southern Hemisphere. At the meeting, researchers laid out fresh details of how that warping might occur. "It's a careful explanation for what's going on in the outer galaxy," comments astrophysicist David Spergel of Princeton University in New Jersey.



CREDIT: NASA/ESA/A. SCHALLER (FOR STSCI); C. SMITH/S. POINTS/MCELS TEAM/NOAO/AURA/NSF; F. WINKLER, MIDDLEBURY COLLEGE/MCELS TEAM/NOAO/AURA/NSF (INSET)

Warped. The Magellanic Clouds, both large and small (*inset*), bend our galaxy's disk of gas and stars.

Important clues came from detailed radio images of neutral hydrogen gas in the Milky Way's disk, assembled by scientists in the Netherlands, Argentina, and Germany. Astronomer Leo Blitz of the University of California, Berkeley, and colleagues used the data to chart the asymmetric ebbs and flows of hydrogen above and below the disk. The team found that it could describe the warped shape as a mathematical superposition of three simple modes of vibration. Effectively, the Milky Way behaves like a vast cymbal anchored at its center.

Then, Blitz and dynamicist Martin Weinberg of the University of Massachusetts, Amherst, constructed a model of how the Magellanic Clouds might excite those vibrational modes. Although the two galaxies contain perhaps 2% of the Milky Way's mass, they exert an outsized influence thanks to one factor: dark matter. The dwarfs loop around our galaxy on lazy orbits lasting 1.5 billion years, slogging through the Milky Way's extended halo of hidden dark matter. Those motions raise persistent gravitational "wakes" that tug on the disk, Blitz says. The forces resonate strongly around the disk's edges, where gas is most loosely bound.

When Weinberg and Blitz ran their model, they were surprised to see the disk's outermost portions constantly flapping as the Magellanic Clouds trundled along. That impressed astronomer Linda Sparke of the University of Wisconsin, Madison, who notes that at least half of all galaxies have distorted disks. "This will help convince people that there are ways to get warps to live a long time," Sparke says. Thorough studies of the Milky Way's warp should let astronomers trace the extent and impacts of the galaxy's shroud of dark matter, she adds.

Astronomer James Binney of Oxford University in the U.K. agrees that "junk" falling onto our galaxy creates lumpy irregularities in its halo and makes the disk quiver. But he thinks it's hasty to finger the Magellanic Clouds exclusively. In particular, a smaller and closer galaxy called the Sagittarius dwarf is now plunging through the Milky Way's disk, so its punch may contribute as well. "Both the dynamics and the astronomy are a bit of a mess," Binney says. "I don't think this story will close off any time soon."

→ ROBERT IRION

Snapshots From The Meeting >>

Bulging waist. Vega, a bright star in the northern sky, barely holds itself together. The combined light from six widely spaced 1-meter telescopes at Mount Wilson, California, resolved fine details on Vega's surface. Interferometry patterns showed that gas at Vega's equator is a whopping 2300 kelvin cooler than at its pole, caused by the star's grossly distorted shape as it rotates once every 12.5 hours. Modeling led by astronomer Jason Aufdenberg of the National Optical Astronomy Observatory in Tucson, Arizona, suggests that Vega would break apart if it spun only 9% faster.

Doomed giants. Infrared telescopes have exposed the heftiest group of the biggest stars. Of about 200 known red supergiants in our Milky Way, 14 reside in a tight cluster previously hidden behind dust toward the galaxy's center (artist's conception, above). Each unstable supergiant is roughly 1000 times as large as our sun. On average, one star should explode in a supernova every 20,000 to 60,000 years, says astronomer Donald Figer of the Rochester Institute of Technology in New York. Recent blasts in the cluster explain a distinct buzz of gamma rays and radio waves from that part of the sky.

Nearly perfect. Those who enjoy geometric beauty in nature will gravitate to PSR J1909-3744, a rapidly spinning pulsar 3700 light-years away. For nearly 2 years, astronomer Bryan Jacoby of the Naval Research Laboratory in Washington, D.C., and colleagues clocked the arrival times of about 19 billion of the pulsar's blips. The accurate timing revealed that the pulsar's orbit, around a tiny companion star, tracks the most circular path yet seen in space. The orbit spans more than 1 million kilometers, but its major axis is just 11 *micrometers* wider than its minor axis.

–R.I.

EDITED BY YUDHIJIT BHATTACHARJEE

On Campus

SKELETONS IN THE CLOSET. A paleontologist at the Burke Museum of Natural History in Seattle, Washington, flouted state and federal permitting laws and cut scientific corners in amassing a major collection of vertebrate fossils. That's the conclusion of a three-person panel brought in to examine the 35-year legacy of John Rensberger, who dug up almost all of the museum's more than 45,000 vertebrate fossils before retiring in 2004.

"Many specimens in the Burke Museum are beautifully preserved and skillfully prepared, but their significance to modern paleontology may have been drastically and perhaps irretrievably reduced" because of incomplete or erroneous information, says the panel, whose 18-page report was released 26 January. The collection "obviously comes up wanting," says panelist Theodore Fremd, head paleontologist for the National Park Service's John Day Fossil Beds National Monument in Oregon.

The University of Washington, which runs the museum, is funding a graduate student to assist the new curator in straightening out the collection. Rensberger, who isn't commenting, has handed over 10 field notebooks dating from 1967 to 2003. "It's going to be a lot of work," Fremd says.

JOBS

NEW MISSION. Space scientist Scott Hubbard will soon begin looking for conditions conducive to extraterrestrial life after an inhospitable climate forced him out as head of NASA's Ames Research Center. On 15 February, Hubbard assumes the Carl Sagan Chair for the Study of Life in the Universe at the SETI Institute, in nearby Mountain View, California, where he'll help expand the institute's astrobiology efforts.

"[NASA Administrator] Michael Griffin and I talked before the holidays and agreed that he should have the ability to pick a center director of his own choosing," says Hubbard, whose replacement at Ames will reportedly be astronomer and retired Air Force Brigadier General Simon P. Worden. Wesley Huntress, director of the Geophysical Laboratory of the Carnegie Institution of Washington, D.C., says that Ames "blossomed" under Hubbard's 3-year directorship: "NASA loses a very good man."

AWARDS

WELCOMING FOREIGN TALENT. A transplanted Spaniard is the first winner of a $50,000 prize to honor immigrant scientists in the United States.

Joan Massagué, 52, of Memorial Sloan-Kettering Cancer Center in New York City has captured the Vilcek Prize in Biomedical Research for his work deciphering metastasis. Massagué came to the United States in 1979 as a postdoc. But instead of returning to Barcelona, he nabbed a faculty position at the University of Massachusetts Medical School in Worcester. "There was no grand plan, no deep vision, just a guy who had some ability," he says, lamenting that tighter U.S. immigration rules discourage young foreign scientists today from pursuing the path he took.

The prize was created by Jan and Marica Vilcek, who fled Communist Czechoslovakia in the 1960s for the United States. Jan Vilcek spent his career at New York University, where he helped invent the blockbuster drug Remicade to treat autoimmune diseases.

POLITICS

PROMISES. Creating more opportunities for young scientists is a top priority for Egypt's new science and higher education minister, a geological engineering professor at Cairo University. Hany Mahfouz Helal, who comes to the post after working on plans for a new science and technology university, hopes to establish centers of excellence in nanotechnology, biotechnology, and information technology.

Pioneers >>

VOICES FROM WITHIN. Unhappy with events at the Centers for Disease Control and Prevention in Atlanta, Georgia, senior staffer Robert Keegan has launched a Web site where employees and CDC watchers can vent. Keegan, deputy director of CDC's Global Immunization Division, says CDC Chatter (www.cdcchatter.net) is "a forum where people can talk" about issues at the agency, including a controversial reorganization begun by CDC Director Julie Gerberding 3 years ago.

Keegan, 53, is one of a few staffers who have openly criticized the reorganization, which some say has driven away many top scientists and managers. Judging from entries posed since the Web log went live on 1 January, the agency hasn't turned the corner yet. Anonymous writers have commented on everything from "ongoing and endless reorganization and resultant chaos" to CDC's "totally embarrassing" response to Hurricane Katrina. A 4% cut in division budgets to pay for Gerberding's management initiative "is causing considerable anger and loss of morale," says one staffer.

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LETTERS

edited by Etta Kavanagh

Reactions to the Hwang Scandal

Chung Myung-Hee, head of the Seoul National University panel that investigated Woo Suk Hwang's work, announces the panel's findings at a press conference on 10 January.

IT CAME AS QUITE A SHOCK TO KOREAN ACADEMICS TO LEARN THAT Woo Suk Hwang's papers on patient-specific stem cells were fabricated. Members of the Korean Society of Molecular and Cellular Biology, the largest life science academic society in Korea, seriously regret that such a fraud could occur. Since the ethical debate over human ovum supply and somatic cell cloning began, our society members have felt very uneasy and frustrated.

Indeed, we decided to establish a charter for scientific conduct with a strong emphasis on the ethical implications of biological research. The life science researcher's charter has been unanimously acknowledged by our members and was declared officially in October 2005 at the annual congress.

The main points of the charter are as follows. First, we have to consider the impact that research may have upon humans, society, and the ecosystem before inititating that research. Second, we have to ensure and respect the dignity of life within the research objectives, from cells to living organisms. Third, we should not fabricate any experimental results and should be righteous in the distribution of materials and results. Finally, we should be fair in acknowledging authorship and intellectual property of research outcomes.

As the president of the Korean Society of Molecular and Cellular Biology, I sincerely regret that such a fraud occurred. A strong policy to prevent any further similar disgraceful incidents will be established. I believe in the ethical sincerity and academic integrity of our scientists, as suggested in the Charter of Ethics for Life Science Researchers, and that we will continue on in our efforts toward bettering society and human life.

SANG CHUL PARK

President of Korean Society of Molecular and Cellular Biology, Department of Biochemistry and Molecular Biology, Seoul National University Medical School, 28 Yon Gon Dong, Chong No Ku, Seoul 110-799, South Korea.

RECENT REVELATIONS REGARDING THE RESEARCH by Woo Suk Hwang and his colleagues on patient-specific embryonic stem cells created by somatic cell nuclear transfer ("Editorial retraction," D. Kennedy, 20 Jan., p. 335) in South Korea undermine the credibility of the nascent, and fragile, stem cell field. These unfortunate circumstances may embolden opponents of embryonic stem cell research who have argued against such research based on moral objections and on mistrust of scientists to monitor their own activities and ambition.

Excesses in high-profile biomedical research are regrettably not new. The history of the gene therapy field provides one perspective. Soon after cloning of mammalian genes first became possible, expectations were raised that gene therapy might be used to treat serious genetic disorders, such as hemoglobin diseases, cystic fibrosis, and cancer among others. After a flurry of initial clinical experiments in gene therapy that led to unsubstantiated claims or lack of objective findings, a panel was convened by the NIH Director Harold Varmus in 1995 to assess the state of the field (*1*). This group described a field in which research findings were oversold, expectations were raised beyond what was reasonable at the time, and scientific rigor was relaxed in the enthusiasm to rush ahead.

If gene therapy and stem cell fields have elements in common, what does recent history suggest for the future? Since 1995, progress in gene therapy has been episodic, yet clearly on a positive trajectory. In an elegant study reported in 2000, Fischer and his colleagues provided evidence for successful gene therapy of X-linked combined immunodeficiency (*2*). Reconstitution of the immune system was sustained. However, a significant setback was encountered by 2003. Several patients developed leukemia due to insertion of the gene therapy vector in an oncogenic locus, a complication that was anticipated as a rare "side effect" but may be addressable with improved vectors. Fortunately, chemotherapy induced remission in these patients. So, while there are potential serious adverse events associated with gene therapy, they need to be weighed against the lethality of the original condition and the capacity to manage the side effects of therapy. Although progress in the clinical arena hasn't matched what was hoped for in the early 1990s, conclusive evidence of efficacy and success has emerged 10 years later.

Except for the use of bone marrow transplantation for the treatment of primary hematological conditions, the stem cell field (as related to treatment of human disease) is in its infancy, perhaps similar to the status of gene therapy nearly 20 years ago. Although we may despair of the recent events unfolding in South Korea, we should take solace from the confidence that strict adherence to scientific rigor and reason will ultimately prevail and permit realization of the potential of stem cells to ameliorate the suffering of patients with life-threatening diseases.

STUART H. ORKIN

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1. See www.nih.gov/news/panelrep.html.
2. M. Cavazzana-Calvo *et al.*, *Science* **288**, 669 (2000).

IT IS APPROPRIATE THAT *SCIENCE* SHOULD LEAD the way in recounting exposure of the fraudulent claims of W. S. Hwang *et al.* that they developed 11 patient-specific cell lines by somatic cell nuclear transfer (SCNT) (D. Kennedy, "Editorial retraction," Letters, 20 Jan., p. 335).

The profoundly negative effect of this episode is all the greater because of the way in which the matter was handled from the outset. When the 2005 paper was received in the *Science* editorial office, it was regarded as a showstopper, something that would make big headlines, with important implications for the treatment of a number of diseases. That much was noted in the News of the Week article "… And how the problems eluded peer reviewers and editors" (J. Couzin, 6 Jan., p. 23), e.g., "[i]mmediately, the journal's editors recognized a submission of potentially explosive importance." The paper was published in due course and hailed in several quarters as important science. But was its science in any way special?

Even if Hwang *et al.* had achieved what they described, all they had done was to repeat with human material what had been done with several other species. At best, it had required skill, persistence, and some technical twists, but nowhere was there evidence of any significant contribution of cell or molecular biology or of concept. Success with other species made it relatively easy to fake, and one cannot blame the journal's referees for failing to recognize that.

If the *Science* editorial staff had paid more attention to the science and less to the sensation, and if others had not leapt onto the bandwagon, the impact of this sorry affair might have been much less.

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THE ROLE OF YOUNG KOREAN RESEARCHERS IN the Hwang controversy ("How young Korean researchers helped unearth a scandal," S. Chong and D. Normile, News of the Week, 6 Jan., p. 22) raises important aspects of research misconduct that are long overdue for international action.

It took the actions of an anonymous whistleblower to unmask the deception and dishonesty of Woo Suk Hwang. It is noteworthy that the whistleblower chose to make his allegations anonymously—even though he was no longer working in the laboratory—and to a TV program and not to the university involved or to regulatory authorities.

The central role of whistleblowers in the Hwang scandal affirms the urgent need for (i) whistleblowing of fraudulent activity to be accepted and encouraged as a legitimate duty that is integral to the responsible conduct of research; (ii) institutional policies that protect the rights of all parties, especially junior researchers, to due process and protection from retribution, intimidation, and harassment; and (iii) an international standard of responsible research and definition of research misconduct.

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Questions About Forensic Science

IN THEIR REVIEW "THE COMING PARADIGM SHIFT in forensic identification science" (5 Aug. 2005, p. 892), M. J. Saks and J. J. Koehler confuse the roles of adversaries in the criminal justice system with those of objective scientists. The "assumption of discernible uniqueness" may seem to be a tenet of forensic science; however, it is not found anywhere in the literature. They claim that "Traditional forensic scientists seek to link crime scene evidence to a single person or object 'to the exclusion of all others in the world.'" Some analyses can never obtain such resolution, and the practitioners of those disciplines would not claim to be able to do so. Those disciplines that do seek to individualize evidence do not adhere to their invented proposition "when a pair of markings is not observably different, criminalists conclude that the marks were made by the same person or object." The references they cite [see their (*7*, *8*)] for this proposition contain no such language. Source attribution rarely, if ever, relies on a single marking.

We take exception with the implication that "all" experts have a propensity to fabricate and lie about evidentiary results. In fact, all comparative forensic science fields have a reasonably high frequency of exclusions. This is in conflict with the notion of data manipulation to achieve unique identification. There is as much incentive in obtaining a true result when it is an exclusion as there is in achieving a match. Fudging a match has dire consequences that the overwhelming majority of forensic scientists appear to support true perpetrator is still free preying on innocent victims and the forensic scientist risks having a contrary (legitimate) scientific opinion presented in court.

Errors do occur in any endeavor involving humans. However, Saks and Koehler do not define the types of error that can occur and describe which ones are of consequence and which are not. Instead, they focus on diminishing the weight of evidence based on a hypothetical error rate that does not apply to the case at hand. Saks and Koehler declare that "the practical value of any particular technology is limited by the extent to which potentially important errors arise" as if this potential necessarily decreases the value of the evidence. A known error rate is not a direct measure of the reliability of the specific result(s) in question. The most direct way to measure the truth of the purported results is to have another expert conduct his/her own review (*1*), as is advocated by the National Research Council for DNA analyses (*2*).

Saks and Koehler misstate many of the false-positive error rates. For example, microscopic hair comparison is estimated at 12%. The Houck and Budowle (*3*) study contains no data on false-positive errors. It is a comparative study of the different resolving capacities of the methods.

When an error of consequence occurs, corrective action is taken. Subsequently, the forensic scientist is better educated and less likely to err. The calculation of a current error rate should take this into consideration. The error should never be ignored, and if the defense believes it useful, it should make use of such information during a cross-examination.

Saks and Koehler did not point to one example of the foundations of the disciplines being baseless; they merely focused on errors having been committed by scientists. Forensic science is evaluating itself and is improving its practices (*4*). Enhancing the forensic disciplines should continue and must be advocated.

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IN THEIR REVIEW "THE COMING PARADIGM SHIFT in forensic identification science" (5 Aug. 2005, p. 892), M. J. Saks and J. J. Koehler assert that error rates in forensic science can be calculated for comparisons performed by human examiners, and that these error rates can then be used to predict the probability that

an error (false match) occurred and thus assess the probative value of the identification for the jury. In fact, the National Research Council concluded that using error rates in such a predictive fashion (especially error rates gathered from proficiency testing) is inappropriate (*1*).

The likelihood of committing an error will be dependent on the complexity of the task, the examiner, and various conditions of the task. In forensic casework, the conditions are varied and we are human and fallible. Proper quality control is imperative to reducing (but not eliminating) the chance of error.

The authors indicated that proficiency test errors of fingerprint experts were "about 4 to 5%" false-positive errors on at least one fingerprint comparison. The manufacturer of these proficiency tests did not report a 4 to 5% "false-positive" error rate (erroneous matches), but rather they reported that 4 to 5% of the answers "differed from the manufacturer's expected results" (*2*), a critical distinction. If an examiner reports "inconclusive" (perhaps they lacked the training and experience to make the match) or records an answer incorrectly (clerical error), this will be reported as "differing from the manufacturer's expected results." This is not a false match as the authors are reporting.

Their fig. 1, which purports to show a disturbingly high incidence of false testimony and forensic testing errors, has not previously been published in any peer-reviewed scientific journal. There is no discussion of the data sampling techniques, methods, or criteria that support this graph.

I have several questions regarding the source of these data: Were the errors attributed to faulty "forensic testing" from a handful of scientists or many? Were these cases and testimonies reviewed by experts qualified to make scientific determinations, or rather by lay people, law students/professors, and Innocence Project volunteers? Of the "forensic testing errors," were these true testing errors or do they simply reflect the limitations of the tests and technology of the era?

I would invite the authors to perform their own research experiments, attend the identification conferences, and become involved in the community that is already performing the research for which they are calling. They will find a new generation of scientifically gifted and objective scientists, skilled at what we do, but interested in discovering new ways to improve it.

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I WAS DISMAYED TO FIND A VARIETY OF ERRORS in the Review by M. J. Saks and J. J. Koehler on forensic identification sciences ("The coming paradigm shift in forensic identification science," 5 Aug. 2005, p. 892). Of chief concern is a spurious fact offered by the authors regarding a paper I co-authored with Bruce Budowle (*1*). In that paper, we reviewed 170 cases in which microscopical and mitochondrial DNA examinations were conducted on hair samples in casework. We found that out of 170 cases, 133 were sufficient for analysis; of these, in only 9 cases did the hairs have a similar microscopic appearance but different mtDNA sequences (6.7%). Nowhere in that paper do we state that error rates "for microscopic hair comparisons are about 12%" as Saks and Koehler quoted in their article. Moreover, the results of our study, although illuminating, cannot be used as an error rate for all forensic microscopical hair comparisons (*2*); the authors state this themselves, citing the National Research Council's publication (*2*), but then go on to do just that for many forensic disciplines.

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IN THEIR REVIEW "THE COMING PARADIGM SHIFT in forensic identification science" (5 Aug. 2005, p. 892), M. J. Saks and J. J. Koehler claim that handwriting error rates on proficiency tests for handwriting experts are between 40% and 100%. What they fail to state is that the tests they are quoting from were given between 1975 and 1985. These initial tests were themselves designed as "tests" to create a fair gauge of proficiency that would also accurately reflect a forensic document examiner's (FDE's) casework. Even so, those in the early 1980s did not recognize the range of conclusions issued by FDEs. Qualified conclusions on the correct side of the opinion scale were incorrectly deemed errors, creating what appears to be a higher error rate. Saks has previously written that the Collaborative Testing Services (CTS) advisory committee informed him that proficiency tests were not suitable for use in gathering data on a forensic discipline (*1*). CTS tests given between 1990 and 2005 reveal that FDEs issued proper conclusions 95 to 100% of the time (error rates between 0 and 5%). The lower error rates are not due to CTS "dumbing down" the tests, but due to tests that more accurately reflect casework and the range of conclusions issued by FDEs. The contemporary CTS tests are in agreement with Moshe Kam's proficiency testing studies (*2–5*).

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Response

THE ESSENTIAL MESSAGE OF OUR REVIEW WAS that forensic individualization/identification science is on course for a "paradigm shift" in which its future will be more scientifically grounded than its past.

Harmon and Budowle take issue with the simple point that traditional forensic science assumes that markings produced by different people and objects are observably different. The notion of uniqueness is widespread in forensic science writing, thinking, and practice. We added the qualifier "discernible" to the uniqueness assumption to indicate that criminalists do not refer to uniqueness in the abstract or as a metaphysical property. They mean that conclusions about object uniqueness are attainable in practice [(*1*), p. 45 and p. 123].

Harmon and Budowle suggest that we claimed that source attribution "relies on a single marking." We said no such thing, as is evident in the sentence they quote. Our point was simply that when criminalists cannot distinguish between two markings—such as two fingerprints—they assume the markings were made by a single person or object.

Harmon and Budowle misrepresent our Review when they say we implied that "all" forensic science experts have a propensity to lie. As we clearly indicated, the word between those quotation marks is that of Andre Moenssens, a former forensic scientist and lifelong supporter of the field. What we did say was that the organizational setting and culture in which many forensic scientists work can create pressures of the sort Moenssens describes. Recent reports of widespread data fudging and fabrication in forensic science provide additional reason for concern [e.g., (*2*, *3*)].

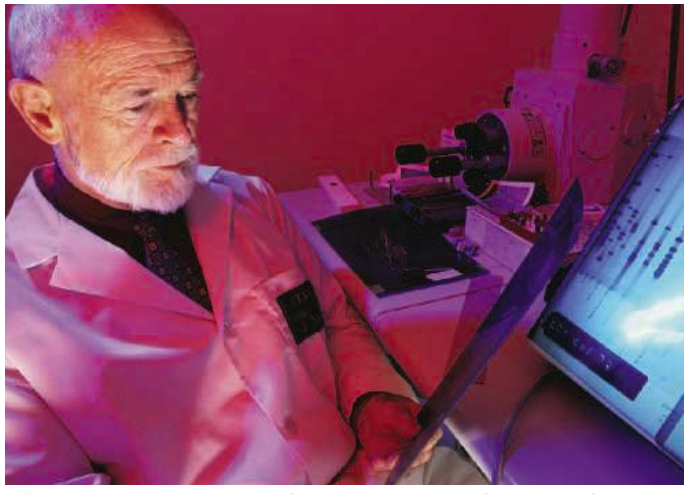
Harmon and Budowle, as well as Langenburg, believe that error rates are not relevant for predicting the chance that an error will occur in an individual case. We addressed this belief in our Review (pp. 894–895) and elsewhere (*4*). It is a fallacy to believe that base rates should be disregarded in individual prediction tasks because they are insufficiently case-specific. From a Bayesian standpoint, the probability of error in a particular case requires an assessment of both the prior probability that the error will occur and the individuating features of the target case. Because the error rate informs the prior probability (and will often be identical to it), it is enormously relevant to an estimate of the chance of error in a particular case. This is one reason why forensic scientists should participate in well-designed proficiency tests on a regular basis. As reliable data from these tests accumulate, it should be possible to take advantage of increasingly refined error rate estimates.

Harmon and Budowle assert that we "did not point to one example of the foundations of the disciplines being baseless [but] merely focused on errors having been committed by scientists." We did not say that forensic science is "baseless." Instead, we identified a series of issues that go to the heart of the status of the traditional forensic sciences as mature sciences. For example, we pointed to forensic individualization science's continued reliance on an unproven and likely untestable 19th-century model of uniqueness. We suggested that the field needs to adopt a more realistic, data-based, and probabilistic approach. We also noted the paucity of basic research on assumptions and lack of applied research on procedures.

Langenburg takes issue with our report that "[a]bout 4 to 5% of examiners committed false-positive errors on at least one latent" in fingerprint proficiency tests conducted during the past decade. He says that 4 to 5% actually represents the rate that answers differed from a manufacturer's expected results. Langenburg is mistaken. Our 4 to 5% estimate is the proportion of analysts who indicated that a latent print matched a finger that it did not match at least one time on the proficiency test. This estimate does not include inconclusives. The proportion of analysts who gave answers that differed from the manufacturer's expected results (i.e., the proportion of analysts who did not correctly identify all latent prints in a test) is much larger, about 25%.

Consider the most recent of many latent print proficiency tests that we relied upon in the paper (*5*). In this test, 259 analysts were provided with 11 latent prints plus known prints from 4 relevant individuals (persons A to D). Seven analysts (3%) committed obvious false-positive errors. Of these, two analysts mistakenly said that a print that belonged to person A belonged to person B; three analysts mistakenly said that prints that should have been marked as unidentified belonged to person C; and two analysts mistakenly matched prints that belonged to persons A and B to people who were not even provided on the test. These are false-positive errors.

One cannot sweep away the mistakes that have been committed by suggesting they are mere clerical errors or the cautious "inconclusives" of novice examiners. Proficiency tests have detected, and continue to detect, significant false-positive errors by latent print examiners. The rate at which these and other errors occur should be tracked, published, and studied to help identify the probative value of reports offered by forensic scientists.



A forensic scientist at George Washington University studies DNA evidence.

CREDIT: RICHARD T. NOWITZ/CORBIS

Langenburg expresses concern about the data on DNA exoneration cases that appear in our fig. 1. As indicated in the Review, the underlying data were provided to us by the Innocence Project, and we relied on those data when computing the proportions associated with the factors in the figure. These data represent all of the DNA exoneration cases that have been coded by the Innocence Project (n = 86 cases) to date. Dozens more cases remain uncoded. Research on DNA exonerations is obviously in its infancy, and we support calls for a more complete and scientific review of these cases.

Houck complains that the 12% error rate we provided for microscopic hair comparisons "using results of mitochondrial DNA testing as the criterion" (p. 895) is not expressly stated in the Houck and Budowle article we cited (*6*). The data in the Houck and Budowle article formed the basis of our computations, just as they did for the new calculation that Houck offers in his Letter.

Table 2 in Houck and Budowle compares the results of 11 laboratories, DNA for support 170 pairs of hairs (known and questioned). Each mode of testing yielded four categories of outcomes: association (the hairs match), exclusion (the hairs don't match), inconclusive, and no exam (unsuitable sample for testing). Omitting the 37 unsuitable pairs, 133 remained. Houck now reports that "in only 9 cases did the hairs have a similar microscopic appearance but different mtDNA sequences (6.7%)" (sic: 9/133 ≈ 6.8%). Even if Houck has sound reasons for deflating the error rate by including 38 inconclusives in his denominator, why not also mention that different conclusions were reached by the two methods 35% of the time (46/133)?

Where ground truth is unavailable, as in Houck and Budowle's study, a conventional approach is to select what is believed to be the best measure as the criterion ("gold standard") against which a measure of interest can be compared. Taking such an approach, how do microscopic hair comparisons stack up against the mtDNA gold standard when conclusions were offered by examiners? One way to report such data is to say that of the 26 cases in which the mtDNA found an exclusion, the examiners using the visual approach called an association 9 times. These data indicate a Type I false-positive error rate of 35% (9/26). Another way to look at the data is to report that 9 times out of the 78 times that visual examiners declared an association (12%), the mtDNA technique showed an exclusion. That is the 12% we reported in our Review.

We did not state that handwriting error rates on proficiency tests are between 40% and 100%, as Kelly claims. We said that the error rate has run as high as 100%, and we should have more clearly indicated that the risk of error on subsequent proficiency tests still ran as high as around 40%.

Kelly correctly notes that, in general, examiners made fewer errors on more recent proficiency tests than they made in the past. What accounts for this performance change? A thoughtful student of this matter has commented: "Have handwriting examiners improved abruptly and markedly? Or did the tests become easier? Most likely, the latter. The test manufacturers describe them as more straightforward, they appear to be simpler, and rather than complaining about test difficulty (as examiners did before the 1990s), examiners now commented about how easy the tests were" [(*7*), p. 69].

The difficulty of the writing task could have an enormous impact on examiners' performance. For example, in one recent test where the items varied in difficulty, examiners were pro-

vided with several handwritten receipts and two known sources (*8*). On one of the receipts, the signature was that of one of the known sources, but the text was produced by neither source. Of 131 examiners, 127 (97%) correctly concluded that the signature "was" or "probably was" that of one of the known sources. But only 25 examiners (19%) correctly excluded both known sources as persons who did not or probably did not write the text of the receipt.

These and other test data suggest that examiner performance varies markedly with the features of the writing task. We therefore support systematic research aimed at mapping the relationship between the varying attributes of writing problems and the circumstances of the examination, and how well examiners perform under those varying conditions. The fruits of such research will provide exactly the kind of information the Supreme Court says trial courts need, namely, guidance for assessing expert performance in the expert "task at hand" (*9*, *10*).

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CORRECTIONS AND CLARIFICATIONS

News Focus: "After the crisis: more questions about prions" by M. Enserink (16 Dec. 2005, p. 1756). This article on synthetic prions reported that the "protein-only" hypothesis is not clinched by the generation of prion infectivity in Claudio Soto's PMCA reaction. The major caveat was described as follows: "because the reaction takes place in a complex, brain-derived chemical mix, one cannot rule out that, say, a small piece of nucleic acid that's essential to infectivity was replicated along with PrP^{Sc} in each cycle." This concern was mistakenly attributed to Byron Caughey, who agrees with Soto's statement that nucleic acid replication under such cell-free conditions is highly unlikely. A more plausible caveat, Caughey suggests, is that a small host-derived nucleic acid, sulfated glycosaminoglycan, or other non-protein molecule might be provided as a component of infectivity in each amplification cycle with the addition of normal brain homogenate.

TECHNICAL COMMENT ABSTRACT

Comment on "Neutral Ecological Theory Reveals Isolation and Rapid Speciation in a Biodiversity Hot Spot"

Rampal S. Etienne, Andrew M. Latimer, John A. Silander Jr., Richard M. Cowling

Latimer *et al*. (Reports, 9 September 2005, p. 1722) used an approximate likelihood function to estimate parameters of Hubbell's neutral model of biodiversity. Reanalysis with the exact likelihood not only yields different estimates but also shows that two similar likelihood maxima for very different parameter combinations can occur. This reveals a limitation of using species abundance data to gain insight into speciation and dispersal.

Full text at www.sciencemag.org/cgi/content/full/311/5761/610b

SCIENCE AND RELIGION

A Compassionate Universe?

Esther Sternberg

As one would expect from Buddhist practice, the 14th Dalai Lama, Tenzin Gyatso, believes that there is a place for compassion in all aspects of life, even within the hallowed halls of science. In his most recent book, *The Universe in a Single Atom: The Convergence of Science and Spirituality*, he uses logic and specific examples to build a case for adding compassion, a broader view, and some degree of subjectivity into what many see as the otherwise sterile, reductionist practice of modern science. But how can this be done? In his far-ranging treatise, the Dalai Lama explores this question as it applies to physics, neuroscience, genetics, and ethics. Using a classic Buddhist approach, he does not provide answers, but—through comparisons and contrasts of Buddhist analytic thought and the scientific method—challenges us to think of our own solutions.

The Universe in a Single Atom
The Convergence of Science and Spirituality
by the Dalai Lama
Morgan Road, New York, 2005. 224 pp. $24.95, C$32.95. ISBN: 0-7679-2066-X.

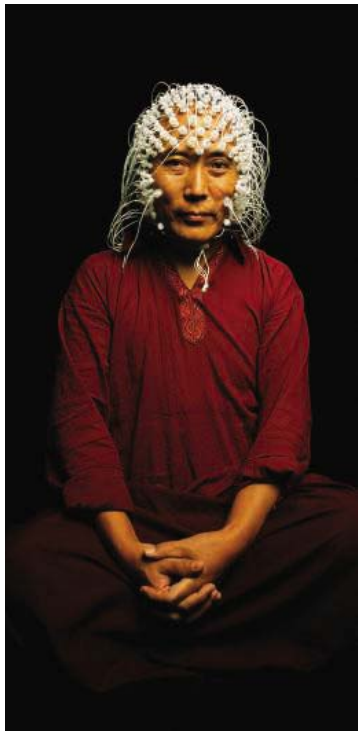
We all know that the scientific method relies on observation, analysis, interpretation, and ultimate conclusions. Those not trained in Buddhist philosophy, however, may not be aware that (as we learn from the book) the same process applies to Buddhist thought. The principal difference is that whereas science starts with an "objective" observation, in Buddhist philosophy, subjective observations are primary. As the Dalai Lama explains, expert meditators are trained to be acutely aware of every momentary sensation, whether arising from the external physical world or the interior landscape of the mind and body. They are then trained to systematically analyze the source of these feelings, to interpret them, and to come to a conclusion using "three methods of verification—experience, inference, and a reliable authority." The author underscores that this process of reasoning is common to the scientific method, although the Buddhist concept of empirical experience also encompasses "meditative states as well as the evidence of the senses."

The Dalai Lama repeatedly decries the excessive reliance on objective and concrete measures in science to the exclusion of the subjective. Although such measures provide a foundation of rigorous modern science, one might indeed question whether scientific observations are truly objective. There are several points at which subjectivity enters the scientific process, including recognition of an event as worthy of study and the moment of insight and understanding. Both are colored by the subjective experience of the observer. Anecdotes abound regarding scientific discoveries in which intuition played a central role in discovery. There is August Kekule's dream of a snake that had seized hold of its own tail, which he claimed had led to his hypothesis of the structure of benzene. Another example is offered by Jonas Salk's story of his discovery of polio vaccine. After laboring fruitlessly for months in his basement laboratory, Salk suddenly solved the problem while in a monastery in Assisi. So convinced was he that the contemplative time he spent in this quiet mountain sanctuary contributed to his discovery that he subsequently (with the architect Louis Kahn) designed the Salk Institute to provide quiet contemplative spaces where scientists could think and work uninterrupted. Perhaps what the Buddhist approach could add to the scientific process, therefore, is an admission by practitioners of science that subjectivity is not all bad and that indeed it can facilitate the process of discovery.

One might conclude that when applied to understanding consciousness, this approach raises the question of whether the object of study—the mind—can accurately assess itself. Modern neuroscience would debate this point, hence the reliance on objective observations derived from quantitative measures of electrical impulses, blood flow, and biochemical changes in different brain regions during different cognitive, behavioral, and emotional conditions. But, the Dalai Lama points out, this currently favored approach, while comforting in its concreteness, still does not explain how thoughts and emotions arise. Whether the author's suggestion that subjective evaluation of the mind by the mind will help to solve the problem remains to be determined.

Is there a place for compassion in science? This is a harder question to answer. Instead of attempting to do so himself, the Dalai Lama challenges us to consider where compassion might fit into the scientific process. At first glance, it would seem hopeless to think that Buddhist compassionate thought could possibly find a place in science, given the radically different goals and approaches of these two world views. The Dalai Lama tells a story that alludes to this difference. A man wounded by a poisoned arrow refuses to allow the surgeon to pull the arrow out but asks numerous questions about the origin of the arrow: "the caste, name, and clan of the man who shot the arrow; whether he is dark, brown, or fair; whether he lives in a village, town, or city; whether the bow used was a longbow or a crossbow … and so forth." Like the stricken man, some basic scientists—those who dismiss observed phenomena in the absence of explanatory mechanisms—would demand to know everything about the arrow (its source, etc.) before acting on the problem. In contrast, the Buddhist approach would emphasize the final and more practical goal of healing the wounded, without necessarily exploring every facet of the problem before doing so.

This divergence between these two world views reminds me of a similar tension that exists between clinical medicine and basic biomedical research. In fact, given their similarities, it is easier to imagine contributions from Buddhist philosophy enhancing clinical practice than basic science. Both the philosophy and the practice rely on subjectivity and intuition—e.g., in clinical practice, making a diagnosis. And compassion clearly plays an important role in clinical medicine, no matter how grounded the treatments are in modern scientific and technical advances. In this sense, perhaps one helpful guide to applying insights gained from Buddhist thought to modern science may lie in the way science and clinical medicine have managed to find a way to comfortably co-exist and comple-



At peace though wired. Richard Davidson and his colleagues at the University of Wisconsin have been measuring brain activity in Tibetan Buddhists in both meditative and nonmeditative states.

CREDIT: CARY WOLINSKI

The reviewer is the author of *The Balance Within: The Science Connecting Health and Emotions*. Web site: www.esthersternberg.com

ment each other's approaches—albeit not without some tensions arising from their different goals and analytic methods.

For many, the most contentious feature of the book may be the author's position as the Dalai Lama. Had the book been written by someone else, it might have been considered a thought-provoking treatise that explores some of the most challenging problems we face regarding the place of science in society. But the book is written by a spiritual leader of millions, one who is not only the ultimate symbol of Buddhism but, its followers believe, the reincarnation of its founder. The very fact that the Dalai Lama chooses to comment on science is already considered by some to be controversial, as evidenced by the protests to his presentation of a keynote address at the recent Society for Neuroscience meeting in Washington, DC.

But in fact, the book falls in the long tradition of treatises by great religious thinkers whose discussions of age-old questions shaped and extended the philosophical scope of their religions. The rabbis of 400 A.D. in Tiberius, whose similar questions and debate led to the compilation of the Talmud, would surely have agreed. So would the Christian philosopher-monks of the 13th century, such as Thomas Aquinas, and Martin Luther. Indeed, if its spiritual leaders do not continue to ask and attempt to answer such questions in light of new discoveries, a religion risks becoming ossified and losing its relevance to modern society. The Dalai Lama makes this point in his discussion of the Buddhist view of Earth and its relation to celestial bodies, whose "sizes, distances [etc.] are flatly contradicted by the empirical evidence of modern astronomy." He suggests that "Buddhism must abandon many aspects of the Abhidharma cosmology," citing the Buddhist dictum that "to uphold a tenet that contradicts reason is to undermine one's credibility; to contradict empirical evidence is a still greater fallacy." This point is sure to be controversial for those who hew more rigidly to Buddhist tradition.

The Dalai Lama, however, does not limit his controversial proposals only to the side of Buddhism. Many scientists may disagree with his plea for including subjectivity and compassion in science. Furthermore, although he clearly supports Darwin's theory of evolution as "a coherent account of the development of life on this planet and the various principles underlying it, such as natural selection," he questions some aspects of the theory. Strict Darwinians may balk at his proposal that the theory falls short on several counts, mainly in its lack of explanations of the origin of life and the origin of "sentience" or consciousness, although the author bolsters his arguments with ample logic. Healthy debate, however, does not require agreement. It simply requires a continuing dialogue, open-mindedness, respect, and thoughtful consideration of other points of view. This is certainly consistent with Buddhist philosophy.

In sum, *The Universe in an Atom* presents a thoughtful plea for scientists to not only delve deeply into a subject but to also stand back and take a broader view of the impact of their discoveries on society—and in so doing, to add compassion to their quest. If we are able to take up the Dalai Lama's challenges, science and society will certainly be the better for it.

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SCIENCE AND LITERATURE

Reading with Selection in Mind

Harold Fromm

Rumor has it that the "science wars" are dead (1). Maybe. Then again, on the same day I began reading *The Literary Animal*, I received the 2005 edition of *Profession*, an annual book-length collection of writings about the state of literary studies from the Modern Language Association (MLA), the flagship organization for literary academics. It opens with a group of essays about science and the humanities, the first of which is by Louis Menand, a literary scholar and well-known writer for *The New Yorker*. Menand remarks,

> Faculty members in science and in social science departments tend to regard humanists as reflexively oppositional to what they do and, therefore, as easy to discount. This perception is founded mainly on ignorance. The summaries of the state of ideas in the humanities in books like E. O. Wilson's *Consilience* and Steven Pinker's *The Blank Slate* are appallingly misinformed.…
>
> The version of the humanities that would make many nonhumanists most comfortable today is the version in which art and literature are ornaments on or neat illustrations of empirical accounts of human life. (*2*)

Moreover, Menand claims that intellectual culture is disposed to a blind faith in "the idea that human behavior is ultimately understandable in biological terms." In the next essay, Barbara Herrnstein Smith, another literary scholar and theorist, criticizes the "scientism" willing to import "one or another currently high-profile scientific or sometimes scientoid program" into the humanities to make them seem less "amateurish" and "impressionistic." She alludes with heavy irony to the Sokal hoax (*3*) and to E. O. Wilson's misbegotten (to her) program to "bridge the gap between the two cultures by integrating the anarchic humanities and the floundering social sciences into the more orderly and grown-up natural sciences…" (*4*).

From where I am sitting, the science wars are looking pretty alive, and now comes a book that is an implied response to the scholars quoted above. *The Literary Animal: Evolution and the Nature of Narrative* is a collection of commissioned essays mostly from the humanities but produced with the editorial blessing of an evolutionary biologist, David Sloan Wilson (Binghamton University). His co-editor, Jonathan Gottschall, received his doctorate in English at Binghamton, where he turned to Wilson and others outside his own unsympathetic department to supervise a thesis that filtered Homer through evolutionary psychology.

The Literary Animal
Evolution and the Nature of Narrative

Jonathan Gottschall and David Sloan Wilson, Eds.

Northwestern University Press, Evanston, IL, 2005. 332 pp. $79.95. ISBN 0-8101-2286-3. Paper, $29.95. ISBN 0-8101-2287-1.

In their introduction to the book's first and longest section, "Evolution and Literary Theory," the editors comment on the blank-slate social constructionism that disparages biological explanations: "the theories of human nature that have dominated literary theory and criticism since the 1960s now only exist in the humanities." Because the editors are acutely aware of their own professional emergence from opposite sides of the science-humanities divide, the interdisciplinary mentality of the essays is markedly warmer and more consciously informed than any attitudes about evolution's usefulness as a tool for literary analysis found among the MLA's typical spokespeople. The volume begins with short forewords by E. O. Wilson and Frederick Crews, eminent maverick voices in the sciences and humanities, and a conciliatory introduction by the editors. These are followed by an essay on human nature by the celebrated novelist Ian McEwan and a benign attempt by David Sloan Wilson to bridge the two cultures of social construction and Darwinian adaptation.

The volume makes a stronger case for consilience than the fledgling anthologies of "biopoetics" (explorations of the arts from the perspective of biological evolution) that began to appear in the 1990s. Far from treating literature as an "ornament," the contributors argue

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for narrative and drama as more or less adaptive. They share a powerful awareness that everything human ultimately derives from the evolved body and brain, no matter how much culture and individual consciousness are capable of varying the forms of expression. So Brian Boyd very plausibly writes that "[e]volutionary analysis of art may or may not, finally, recognize art as an adaptation, but it will almost certainly show that art depends deeply on evolved features of human minds and behavior." Yet however adaptive the arts may be, the threat of biological determinism is a hollow fear, for "[n]o one was ever 'genetically determined' to write or read something as unprecedented as *Ulysses*."

Dylan Evans, originally a Lacanian psychoanalyst who wrote a major guidebook to understanding his mentor, describes the transformation that resulted from his gradual recognition of the evolutionary adaptions generating consciousness and the psychogenesis of his own startling defection. He then provides an account of Lacan's flawed intellectual development. In his essay "From Lacan to Darwin," he writes, "Lacan's ideas are hopelessly inadequate because they are predicated on a false theory of human nature." Because the "value of Lacan's work lay not in any ability to describe the facts, but in its power to produce novel ways of interpreting literary texts," it is mainly literary scholars who still cling to this increasingly repudiated body of work. Evans's attendance at the Darwin Seminars of the London School of Economics during his loss of professional faith produced the requisite "aha!" moment: a recognition of the social sciences' "shaky creationist notion of a radical gap between humans and other animals." Evans subsequently gave up his practice and turned his attention to evolutionary psychology, robotics, and artificial intelligence.

When it appeared in 1995, Joseph Carroll's *Evolution and Literary Theory* (*5*) intensified the growing interest in Darwinian criticism, and Carroll followed it with a paradigmatic collection of essays on the topic (*6*). Here, in "Human Nature and Literary Meaning," he refines evolutionary psychology's mapping of specific modules for human faculties by stressing the role of domain-general intelligence and life-history analysis in accounting for human development and flexibility. With his characteristic skill at reading literary texts, Carroll examines Jane Austen's *Pride and Prejudice*. His analysis demonstrates the insights of a Darwinian social science that can provide literary criticism with "conscious theoretical access to the elemental forces that have impelled all human beings throughout time and that have fundamentally informed the observations and reflections of all writers and all readers."

For years, scholars in the literary humanities have struggled to achieve at least a semblance of the certitude possible in the sciences, although none of the major schools of analysis—whether Freudian, mythic, Marxian, deconstructive, or socially constructive—could make a claim to the sort of falsifiability that quickly winnows scientific theories. But a running theme throughout *The Literary Animal* is the need for quantitative methods that could provide solid foundations for philosophical and aesthetic claims. Gottschall's essay confronts this problem head-on in an eloquent explication of "quantifying the not easily quantifiable" that precedes his report of a test of claims that European fairy tales reflect arbitrary gender norms of western patriarchal societies. He and his student-researchers coded 1440 fairy tales from around the world for explicit and implicit assumptions about the sexual characteristics of protagonists and antagonists, heroes and villains, males and females. Putting to rest (they hope) the impressionistic underpinnings of the gender wars, they found that in tales from societies ranging from the most insular bands and tribes to the most industrialized states, men and women were sexually characterized pretty much as they are in the West.

Will the evolutionary insights about the arts provided in *The Literary Animal* raise the consciousness of Menand, Smith, and colleagues and finally bring the science wars to an overdue end? Check back at the MLA's annual convention around 2010 for the latest developments. I hope we will then find, as Tennyson put it, "The old order changeth, yielding place to new, / And God fulfils himself in many ways."

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BROWSING

The Past from Above. Aerial Photographs of Archaeological Sites. Charlotte Trümpler, Ed. [Photographs by Georg Gerster.] J. Paul Getty Museum, Los Angeles, 2005. 415 pp. $65. ISBN 0-89236-817-9. Frances Lincoln, London. £50. ISBN 0-7122-2478-1. Originally published under the title *Flug in die Vergangenheit* (Schirmer/Mosel, Munich, 2003). Translated by Stewart Spencer.

Gerster has spent the last half-century capturing on film aerial views of ancient monuments from around the world. This volume presents 249 of his images, organized in thematic chapters on villages—such as the settlement mound of Tepe Yahya (right), from the 4th millennium BC in southern Iran—palaces, fortifications, sacred sites, etc. Explanatory notes for the sites (written by archaeologists) are gathered at the end of each chapter. Trümpler's introductory essay spotlights the pioneers of aerial photography in archaeology.

RESEARCH CONDUCT

Lessons of the Stem Cell Scandal

The finding of fraud associated with the Hwang *et al*. stem cell reports raises issues that need careful scrutiny: authorship, ethics, funding, and science education.

Mildred K. Cho,* Glenn McGee, David Magnus*

It has been a shock that dramatic breakthroughs in stem cell research using somatic cell nuclear transfer (SCNT) reported by Hwang and his colleagues in South Korea were largely a product of fraud (*1*). In response, there has been a great deal of soul searching within the scientific community. How could this have happened? Why didn't the peer-review process uncover the fabrication? Do we need to make changes in the way that we conduct and publish research? Rather than putting the way we evaluate research under a microscope, the research community in Korea and elsewhere needs to look at broader, institutional factors contributing to the behaviors that have caused so much dismay in the scientific world.

In the 17th century, trust and integrity in science were central to the system of publication that we have inherited (*2*–*4*). For example, the scientific community had to decide which reports from explorers from distant parts of the globe were reliable. The issue also arose for the emerging experimental sciences, which Boyle and his colleagues at the Royal Society of London argued depended on actually witnessing the experimental events (*3*). Boyle created the precursor to the modern scientific publication to provide sufficient detail so that other scientists could replicate the experiments, thus adding witnesses to the experimental data. In cases where this was impractical, it would serve to produce sufficient information so that the readers were "virtual witnesses" (*3*, *4*).

An important part of 17th-century scientific epistemology concerned establishing how one could tell that the reports were worth believing. This included information about the skill of purported "witnesses," design of the author, internal consistency of the account given, and whether contradictory "testimony" existed in the scientific literature (*5*). Perhaps the most important protection was the integrity of the "informant," Therefore, establishing the rules by which one was trustworthy (a "gentleman") became critical.

We are the heirs of this system. It is not practical or even possible to investigate in detail each submission to each scientific journal, and even investigation after publication can be difficult (*6*). Science must continue to depend on the integrity of its practitioners. It will always remain possible for a skilled practitioner to (at least temporarily) perpetrate fraud. As in the 17th century, replication will remain a key confirmation of purported results. The antiquated notion of the gentleman scientist is no longer applicable or desirable. What is needed is better articulation of the meaning of integrity and how to foster virtue in scientists. It is here that institutional structures in South Korea failed.

In the case of Hwang *et al*.'s research, basic tenets of individual integrity (intellectual honesty and accuracy in representing contributions to research) were violated. Not only were data fabricated (*1*), but there were fundamental misunderstandings among the researchers about their responsibilities as authors. For example, the inclusion of a high-level government official who did not conduct the research (*7*) was inappropriate. Authors provide the authority of a publication and take responsibility for its authenticity. The attempt by the U.S. scientist Gerald Schatten to remove himself as author was also inappropriate, especially because his avowed contribution to the article was to the overall analysis and preparation for publication (*8*).

In complex, interdisciplinary research, coauthors must often rely on each other to vouch for authenticity. The International Committee of Medical Journal Editors guidelines for authorship implicitly acknowledge this in stating that that "Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content" (*9*). Adopting the concept of a "contributor" advanced by Rennie *et al*. (*10*) would clarify and increase the accountability of individual authors. Rennie *et al*. also proposed the concept of a "guarantor" of a publication, an individual who takes full responsibility for the integrity of the entire publication. The guarantor model only works, however, in an environment where colleagues (especially junior scientists and staff) are free to probe and challenge results.

This underscores the importance of other facets of individual integrity—collegiality, communication, and sharing of resources. It has been speculated that a large, compartmentalized laboratory structure could have contributed to the ability to falsify data (*8*). Such structures, while perhaps encouraging efficiency, could inhibit free flow of information and dilute responsibility for the integrity of the work.

The actions of individual researchers do not exist in a vacuum but are affected by institutional factors (*11*). In South Korea, there was awareness of the need for ethical guidelines for research, as evidenced by the recent passage of laws about stem cell research and human subjects (*12*). However, the science may have been moving much more quickly than the ethical standards could be absorbed. For example, it was reported that 85% of over 900 biotechnology researchers surveyed in South Korea did not know what the Declaration of Helsinki was, and that 42% did not know about Institutional Review Boards (*13*). This study was conducted only in Korea, but may be indicative of an international problem. All research institutions need to assess awareness of ethical standards.

The Korean government reportedly provided Hwang's laboratory with upwards of $65 million in a relatively short period of time for research and new facilities, earmarking over ~$25 million in a single year (*14*), and a large research award as a "supreme scientist" (*15*). Concentrated funding of a single laboratory is not likely to foster the growth of a community necessary to build a new research field. Broader, merit-based funding contributes to scientific integrity by encouraging multiple laboratories to develop similar expertise and to better assess each other's results. Large amounts of funding concentrated in a small number of researchers could promote unhealthy competition by the inordinate pressure created by expectations of returns for such large sums.

The alleged fraud in stem cell research sheds light on another area of potential concern. U.S. policies (*16*, *17*) allow, and perhaps even encourage, deidentification of human biological materials when transferred between researchers, to protect privacy and confidentiality of research subjects. However, if identifiers of research materials are irreversibly removed, it could be difficult or even impossible to reevaluate the validity of the results obtained with them. In the Hwang case, for example, if the stem cell lines had been made anonymous, with codes linking patient identities to cell lines destroyed, and if original donor tissues or materials were lost or completely consumed in the course of the research, it would be impossible to conduct an investigation to determine validity.

In addition, researchers who collect tissue samples do not necessarily know what happens to them in downstream research. Researchers who use the donated tissues do not necessarily know how the tissues were collected or whether the collection was done appropriately (*18*). For example, Sung Il Roh, a coauthor of Hwang's, reportedly admitted to paying for eggs, and to doing so without informing Hwang (*19*). Policies intended to protect research subjects might have weakened some of the institutional structures that encourage research integrity by inhibiting communication between scientists

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and a shared sense of responsibility.

According to a newspaper report, Korea's National Board of Bioethics indicated that, in contrast to claims by Hwang's group, information on serious risks of egg donation were not provided to all donors, and that 16 of 100 donors required in-hospital treatment of adverse effects from the procedure (*20*). Even the most stringent regulations also rely on trust.

The responsibilities to mentor students in navigating the pressures of becoming a scientist can pale by comparison to the drumbeat of competition and the expectation to produce. Contemporary research is nested in a plethora of codes, rules, and laws. It is a challenge to inculcate the skills of responsible research let alone the more general set of nontechnical skills and virtues that ennoble science.

Although some research universities now require that doctoral and postdoctoral students complete fairly elaborate courses in ethics, many more treat students to a sandbox morality lesson consisting of the admonition not to lie, cheat, or steal data. The courses may have little effect on future misconduct (*19*). The idea that research training, such as that required in the United States for some federally funded trainees and emphasized by the National Research Council report (*21*), in itself would have prevented fabrication on such a grand scale in South Korea strains credibility.

Teachers must themselves be judged by the authorities in our institutions—not only for their ability to produce science, but also to be scientists of virtue and integrity. The ability to give testimony and to act as a witness can be modeled, and students should be allowed to exercise skills of discernment and skepticism about results that seem unlikely or behaviors that are worrisome without punishment. The lesson to be learned is that we need to do a better job of holding research institutions accountable for setting up systems and mentorship that will produce integrity in its scientists.

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PUBLIC HEALTH

Community Studies for Vaccinating Schoolchildren Against Influenza

A plan to vaccinate schoolchildren against flu presents an opportunity to assess risks and benefits.

M. Elizabeth Halloran* and Ira M. Longini Jr.

The Advisory Committee on Immunization Practices and several states are considering recommending annual influenza vaccination in groups beyond the currently recommended high-risk groups. This offers an opportunity that should not be missed: to conduct a nationwide study of the effectiveness of vaccinating schoolchildren against influenza as a means of reducing community transmission. Some public health officials speak of universal vaccination against influenza, meaning a recommendation for all age groups, but schoolchildren, aged 5 to 18 years, are a prime target as they are generally considered to be the most important source of community-wide transmission. Researchers also believe that the immune systems of children respond better to influenza vaccination than do those in the elderly at-risk population. To realize maximum benefit from a study of such effects, we must prospectively sort out the crucial features to be evaluated: effectiveness, benefits, risks, and costs.

Highly pathogenic avian influenza A (H5N1) and its potential to unleash a pandemic are recently in the news. Aside from reducing community-wide transmission of seasonal influenza, vaccinating schoolchildren against influenza and putting its evaluation into place would prepare us for an organized response to an influenza pandemic, whenever it occurs. Our predictions suggest that if limited doses of vaccine were available, as might be expected during a pandemic, vaccinating schoolchildren would be the most efficient approach to reducing overall numbers of influenza cases.

A combination of vaccinating schoolchildren and older adults would be most effective for reducing influenza deaths (*1, 2*) Results from influenza simulations that we have conducted indicate that vaccinating just 20% of the schoolchildren would do more in reducing overall mortality in adults over 65 years old than vaccinating 90% of the adults over 65 years of age (see chart, page 616, top). Even though schoolchildren and young adults have not been considered at high risk of dying of influenza, annual morbidity is still high, with illness attack rates in schoolchildren exceeding 10% most years. Thus, the benefits would not be limited to the older population.

Expanding annual influenza vaccination would give vaccine manufacturers the incentive of a guaranteed market so that they would be willing to increase production capacity and stabilize the influenza vaccine pipeline. This improves our preparedness for a pandemic strain.

Arguments against and hindrances to vaccinating schoolchildren against influenza need to be taken seriously. Despite the benefits, children already receive many vaccinations, and parents and children balk at the idea of yet another, especially if needed annually. However, even if coverage were incomplete, community-wide benefits could be obtained provided that vaccination rates were 50% or higher, not to mention the direct protection of the vaccinated children. Use of a nasally administered live-attenuated influenza vaccine (LAIV) (*3*) might be an alternative to the traditional shots with killed vaccine. Influenza

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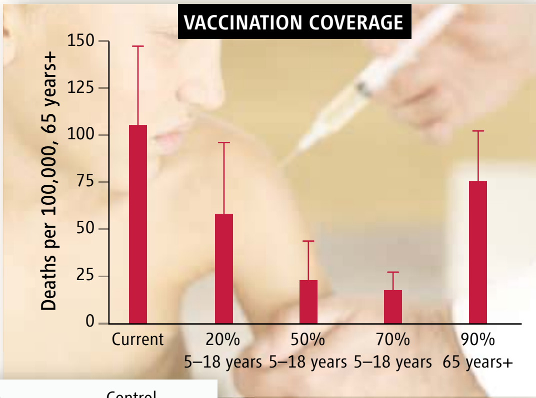
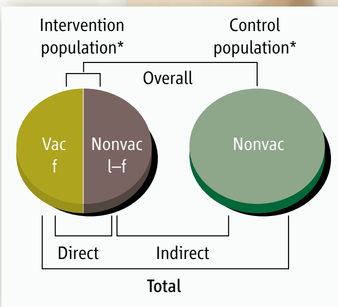
vaccination is generally safe, with mild local reactions, such as soreness at the injection site with the killed vaccine, or runny nose with the LAIV, and, especially in persons with no previous exposure to influenza virus antigen, mild systemic reactions such as myalgia, fever, and malaise (*4*). Guillain-Barré syndrome was associated with the 1976 swine influenza vaccine, but not proven in later vaccines (*4, 5*). Numerous logistical uncertainties remain to be worked out. Who would pay for the additional immunizations? Would distribution be through schools or physicians' offices? Who would carry the liability protection for potential or alleged injury due to vaccination?





Simulated effects of vaccine interventions and study designs. (**Top**) Simulated mean number of deaths per 100,000 in the elderly population and 90% upper confidence limits under the current vaccination coverage in the United States and under different additional levels of coverage in school-aged children or the elderly. The current coverage in the United States is about 5% in children aged 5 to 18 years, 23% in adults aged 19 to 64 years, and 68% in the elderly aged 65+ years. Simulations based on model described in (*5*). (**Bottom**) Types of effects of interventions against infectious disease and different study designs based on comparison populations for their evaluation [adapted from (*10*)].

We are not starting on a blank page. Attempts have been made before to demonstrate the community-wide effectiveness of vaccinating schoolchildren against influenza. Just before the epidemic in 1968, Monto and colleagues vaccinated 85% of the school-age children in Tecumseh, Michigan, against influenza, which resulted in a 67% decrease in the influenza-like illness attack rate in Tecumseh compared with neighboring Adrian (*6*). In an ongoing community vaccination study in Central Texas with LAIV, Glezen and colleagues are attempting to demonstrate that vaccinating schoolchildren reduces the incidence of influenza-like illness in adults (*7*). Although these studies are rigorous, they each have only one or two comparison communities.

A larger-scale study with numerous comparison communities is needed. A study in several schools in the former Soviet Union used a nonspecific outcome as well, so the results are difficult to interpret (*8*). A compelling example of the need to plan evaluation prospectively is provided by the Japanese national vaccination strategy, which, for over two decades until 1987, was targeted at schoolchildren precisely to reduce epidemic influenza. A retrospective reassessment suggesting that the Japanese strategy reduced excess deaths among elderly adults (*9*) is open to criticism because it is based on nonspecific mortality data over time. The time trends could result from factors not related to influenza vaccination. More recently, the province of Ontario, Canada, has been promoting widespread vaccination for all age groups. The analysis of the Ontario experience suffers from weaknesses similar to that of the Japanese. A recent review of 14 studies concluded that further evidence is needed of the indirect effects of influenza vaccination in children (*10*). Although mathematical models of the population-level effects of vaccination offer useful guidance, they cannot replace data from an actual study.

So, what are essential aspects of a successful study? The primary goal has to be evaluating whether increased coverage in schoolchildren would reduce the overall influenza illness attack and death rates in the community as a whole. Comparisons should be made between places where expanded coverage was implemented and those where current recommendations remained in place (see chart, this page, bottom) (*11*). Although we could propose simply vaccinating children in half the states in the first year, followed by the rest of the states the next, it is neither feasible nor desirable. More tractable units of coverage are school districts, communities, cities, counties, or individual states. Enough pairs of units must be included to ensure that the study has statistical power to detect and estimate an effect. The more units are included in the study, the smaller is the chance that any observed differences in influenza incidence would be due to chance. Also, to allow for the possibility that, one year, the vaccine might be mismatched to the circulating strains or that the influenza season is particularly mild, the study should be continued for two or more years. This would also allow progressive inclusion of more communities. Such a geographically staggered introduction would permit vaccine production to ramp up for the increased demand and would give time to monitor potential safety concerns.

A vital factor in the success of such a study is the accurate and consistent diagnosis of influenza. Currently, influenza incidence is measured using nonspecific case definitions, such as pneumonia and influenza-like illness. If virologic confirmation of a random sample of influenza-like cases is done, the proportion of confirmed influenza-positive cases can be used to estimate the proportion of the nonspecific influenza-like cases that were in fact truly influenza (*12, 13*). The importance of virologic confirmation in obtaining accurate estimates is highlighted by the Texas study above in which the direct protective efficacy of LAIV was estimated to be 18% (95% CI: 11, 24) by using a nonspe- cific case definition, and 79% (95% CI: 51, 91) when surveillance cultures were included (*13*).

Many people alive today remember the large mobilization in the 1950s for the polio vaccine trials. Two important differences are that a study of the effect of vaccinating schoolchildren against influenza would involve a licensed rather than an experimental vaccine and would measure the overall effects on reducing transmission, morbidity, and mortality, rather than just the direct protective effects.

We propose nationwide mobilization for a study of influenza vaccination. Similar to the polio vaccine study (*14*), a large study of influenza vaccination will need to be conducted by a partnership of academia, government, and industry. Government could provide the public health access, guidance in operations, and policy, as well as some funding for the research. Industry could provide vaccine and guidance in safety evaluation. Academia could provide expertise in innovative design and central coordination of the study.

Vaccination of schoolchildren will be a massive effort if introduced nationwide. Why not plan for its proper evaluation now?

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NEUROSCIENCE

What's in a Face?

Nancy Kanwisher

Is the primate brain a generalized machine that can tackle a wide array of problems or a collection of modules, each designed for a specific task? New results suggest a modular organization, at least for specialized cognition.

Is the human brain like a Swiss Army knife (*1*), composed of special-purpose components, each tailored to solve a single specific task? Or do we instead possess a more general kind of intelligence, with minds and brains that are prepared to tackle a wide range of problems without being optimized for any of them in particular? For nearly two centuries, a debate has raged between proponents of specialized "organs" or "modules" of the mind and brain and those who support "distributed" cognitive and neural processing. A new study by Tsao *et al.* on page 670 of this issue (*2*) provides the strongest evidence to date for the Swiss Army knife view by demonstrating the extreme specificity of one cortical region for a single high-level function—face perception.

Tsao *et al*. used functional magnetic resonance imaging (fMRI), a noninvasive neuroimaging technique for studying brain activity, to identify three patches of cortex in monkeys that respond selectively to faces. They further targeted electrodes into the "middle face patch" (see the figure) to record from the individual neurons that constitute it. Their findings give astonishing evidence of functional specialization in the brain. Ninety-seven percent of visually responsive neurons in this region responded selectively to faces, and whoppingly so: On average, these neurons responded more strongly to face stimuli than to nonface stimuli by a factor of about 50. Indeed, the only nonface stimuli that elicited a significant (though very weak) response from this region were apples, clock faces, and other round objects similar in shape to faces.

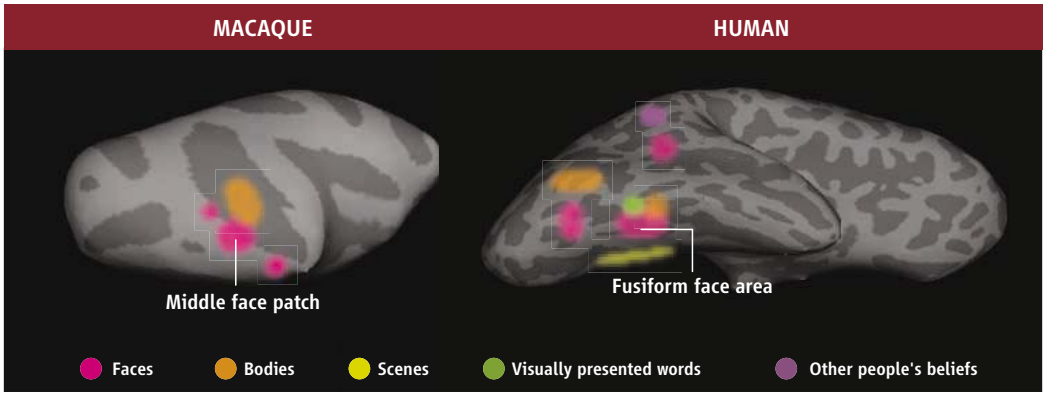
Prior evidence that face perception may be a "special" domain of cognition, with its own independent cognitive and neural machinery, comes from behavioral studies of normal and brain-damaged individuals and electrical recordings of neural activity in monkey and human brains. More recently, fMRI has revealed a particular region in the human brain where this special face perception machinery apparently resides: the fusiform face area, a blueberry-sized region on the bottom surface of the posterior right hemisphere that responds significantly more strongly when people look at faces than when they look at any other stimulus class yet tested (*3*).

The fusiform face area has served as a compelling icon for those inclined toward a modular view of mind and brain, and also as a tempting target on which opponents of this view can fix their cross-hairs. In one of the most important challenges to the claimed specificity of this brain region for faces, it has been argued that the weak but statistically significant response of the fusiform face area to nonface objects reflects the participation of this region in the representation of objects (*4*). An alternative account argues that this weak response to nonface objects simply reflects the resolution limits of the fMRI method, in which each pixel spans hundreds of thousands of neurons. This leads to an inevitable underestimation of the true selectivity of the region. The Tsao *et al.* study largely resolves this question, at least for the middle face patch in the macaque brain. By demonstrating that nearly all cells in this region respond virtually exclusively to faces, these data leave little room for a role of this region in the representation of nonface objects (*4*). Thus, Tsao *et al*. provide the strongest evidence yet for extreme specificity of a cortical region for a complex high-level function.

The new findings open up a broad new landscape of investigation. How exactly do neurons in this region code for the unique shape of each individual face? Does the neural representation of face shape differ qualitatively from the neural representation of object shape, as suggested by the behavioral literature (*5*)? How do the other two face-selective patches in monkeys differ from the one analyzed by Tsao *et al.*, and which of these face patches (if any) is homologous to the fusiform face area in humans?

More generally, which functions get their own dedicated patch of cortex, and why? In addition to face areas, other regions of the human brain (see the figure) produce similarly selective fMRI responses to bodies and scenes (*6*) and even to the representation of another person's beliefs (*7*). But such highly specialized regions may be rare in the cortex: A recent study that tested for the selectivity of 20 different object categories did not turn up any new ones (*6*). In addition to a few highly specialized mechanisms for special domains of cognition—the neural equivalent of an army knife's corkscrew, scissors, and screwdriver—the brain may also contain more general-purpose machinery that can operate across cognitive domains.

Evolutionary psychologists argue that the components of the human mind can be predicted from the specific problems faced by our ancestors on the savannah. But such considerations underconstrain the organization of the human brain. They also fail to explain observed components of the brain that could not be genetically hard-wired, such as the cortical region that responds very selectively to visually presented words and letter strings (which have arisen only very recently in human history) (*8*). Specialized neural machinery may be better predicted by the degree to which the particular task poses unique computational challenges. Perhaps we need special machinery for face perception because faces are the only stimuli requiring discrimination between thousands of exemplars that all share the same basic structure. And perhaps these "face neurons" are clustered together into their own patch of cortex to facilitate interactions between them, either to sharpen their selectivity through mutual inhibition or to medi-



Selective information processing in the brain. Regions on the surface of the macaque (**left**) and human (**right**) brain that respond selectively, as indicated. For both species, the back of the brain is at the left. Brains are not proportionally scaled to each other.

CREDIT: D. TSAO/HARVARD MEDICAL SCHOOL; C. I. BAKER AND R. F. SCHWARZLOSE/ MASSACHUSETTS INSTITUTE OF TECHNOLOGY

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ate one of the key signatures of face processing discovered long ago by psychologists, in which the representation of each part of a face is affected by the presence of other parts of the same face (*5*).

Tsao *et al*.'s stunning data show the power of their new method: fMRI-guided neurophysiology enabled them to find the cortical "sweet spot" in which an unprecedented 97% of cells were face-selective, whereas earlier studies conducted without such guidance estimated that at most 20 to 30% of cells in any given region would be face-selective. This distinction will not be lost on neurophysiologists, and fMRI-guided neurophysiology may soon become standard practice in the field. A further contribution of the present study is the finding of parallel and consistent results from both physiology and fMRI, strengthening the evidence that responses observed by fMRI are closely tied to neural activity. Taken together, Tsao *et al*.'s findings herald a powerful new synergy between neurophysiology and imaging-based research on high-level vision.

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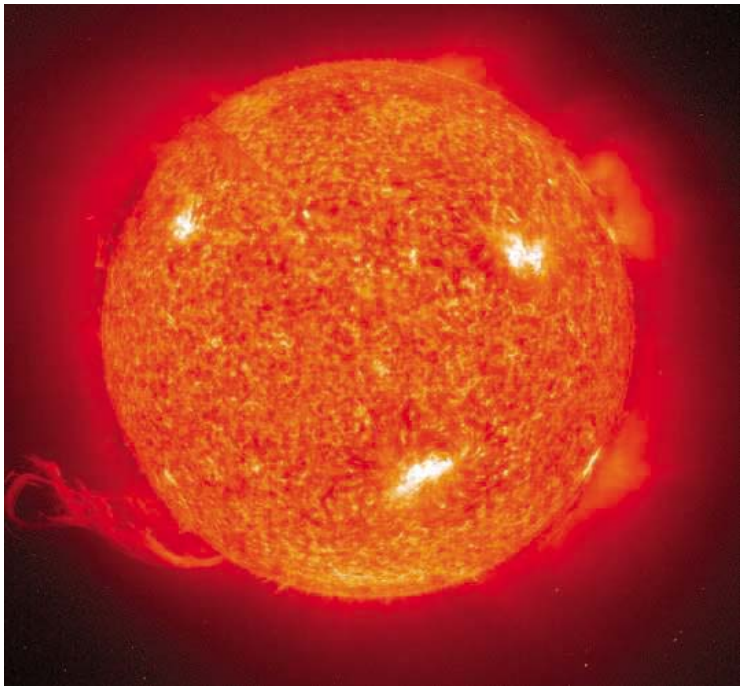
ASTRONOMY

Big Fields on Small Stars

Gibor Basri

Magnetic fields from cool stars have been difficult to study. Now, Doppler imaging methods reveal unexpected details of stellar magnetism and the internal mechanisms of stars such as the Sun.

Magnetic fields are pervasive throughout the cosmos. Most of the matter in the universe is a plasma (a gas of charged particles), and thus influenced by electric currents that can give rise to magnetic fields. Such fields are responsible for phenomena as diverse as Earth's aurorae, the solar corona, spectacular bipolar jets of material shooting from newly forming stars or accreting black holes, and the magnetization that suffuses whole galaxies. Angular momentum is also pervasive in the cosmos, and combined with a moving conducting fluid or plasma it can power a magnetic dynamo. For instance, Earth's core contains one example of a self-generating magnetic dynamo, and our Sun's envelope has another. Indeed, most stars manage to generate magnetic fields, because they are rotating, convecting, conducting bodies. Nonetheless, stellar magnetic fields are notoriously difficult to study directly. On page 633 of this issue, Donati *et al.* (*1*) report an extension of a subtle technique for mapping surface magnetic fields to a very important class of stars.



Solar activity. An image of the magnetically heated surface of our Sun, obtained by the Extreme Ultraviolet Imaging Telescope (EIT) on the Solar and Heliospheric Observatory (SOHO) satellite, provides an impression of what magnetic fields on even fully convective stars may look like (*3*).

It is often said that we live around an average star. This is not really true. Our Sun is about three times as massive as the average star, nearly twice as hot at its surface, and about 100 times as bright. These average stars ("M stars" in astronomers' parlance) are more than five times as numerous as stars like our Sun, and so constitute most of our stellar neighbors. Despite their plenitude, they have received less attention from astronomers than other stars, because until recently they were too faint to be detected by many of the diagnostic techniques applied to stars (for instance, you cannot see any of them with your naked eye even though the closest star to us is an M star).

Convection in stars arises when it is more efficient to transfer energy by mechanical motions rather than simply radiating it outward through stable plasma. The conditions that favor convection arise when the resistance (opacity) of the material to radiation is too high. This tends to happen in cooler material, where there are many more sources of opacity than in fully ionized plasma. Thus, in stars cooler than the Sun, the convection zone deepens to larger percentages of the volume.

The magnetic dynamo created by this kind of convection in our Sun reverses every 11 years, giving rise to the well-known solar cycle. It is thought to arise predominantly at the bottom of the solar convective zone (about 30% of the way to the core), where there is a shear layer between the convective envelope and radiative core. A star with mass about a third of our Sun's will be sufficiently cool that its entire interior is convective. Obviously, the magnetic dynamo must change if there is no radiative core. The expectation is that only a turbulent dynamo will remain, and such a dynamo might only generate small-scale fields (more like what is seen at the minimum of the solar cycle).

The Sun is the only star whose surface we can at present image in any detail (see the figure). For other stars, we usually make do with proxy indicators of magnetic fields related to the heating that they cause in a stellar atmosphere. This heating arises partly because the fields emerge in bipolar regions that are jostled about by the convective motions (not to mention intruded upon by other regions of opposite polarity), causing currents and magnetic dissipation. We thus have a reasonable idea of how the total magnetic flux varies with stellar parameters (through observations of stellar spectra and x-ray luminosities). To actually measure the strength of a stellar magnetic field, determine

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how much of the star's surface is covered by it, or obtain information about its surface distribution is very hard. We rely mostly on the effect the field has on atomic transitions—causing a spreading of magnetic subcomponents in some spectral lines (Zeeman broadening) or changing their polarizations. These diagnostics require high-precision spectroscopy and polarimetry, which are difficult in faint stars.

To make matters worse, one can only work with the integrated light from the whole star. For Zeeman broadening, this means that other forms of spectral line broadening are competing effects. Not only is there thermal and turbulent broadening, but the rotation of the star can produce Doppler broadening (one side of the star is coming toward the observer and the other side receding). Typically the magnetic broadening is comparable to, or swamped by, these other forms of broadening. However, when the star is spinning rapidly enough that the Doppler broadening is much larger than the other forms, it changes from an impediment to an advantage. If there is a magnetic region on one part of the star (for example, a large starspot), its effect will be confined to the part of the spectral lines with the right Doppler shift. This allows Doppler imaging of the surface of a star—a 20-year-old technique that allows us to make maps of stars that are otherwise completely hopeless for imaging (*2*).

To use polarization to study magnetic fields presents another problem. Opposite polarities cancel each other when the light is added together over the whole stellar surface. Because stellar fields tend to be complex, the net polarization signal is often far weaker than the magnetic fields themselves, and usually undetectable. Doppler imaging can help here again, by shifting opposite polarities to different parts of the spectral line if the polarities are sufficiently separated on the stellar surface. This is the method employed by Donati. The fact that they obtain any polarization map at all already shows that there must be large-scale fields on the rapidly rotating M star that they study (though they undoubtedly are missing smaller-scale fields). Both the scale and configuration of the field that they see challenge our expectations, and the predictions of some dynamo models for fully convective stars. Dynamo theory is in a rather crude state, particularly for turbulent dynamos. It is welcome progress that observers will now be able to better constrain the theories for what might be the single most common type of magnetic dynamo in the universe.

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CHEMISTRY

Better Asymmetric Reactions

Molecules of a single chiral handedness are vital in research and industry. New kinds of catalysts are improving the reactions that produce them.

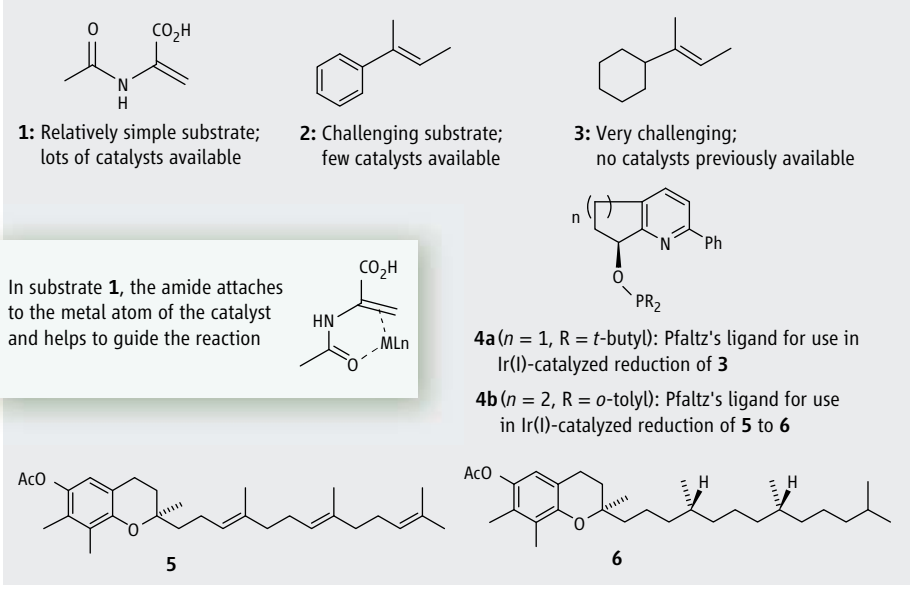
Martin Wills

Look at your hands; now try to superimpose them (palms up). It is impossible, because your hands are examples of chiral structures—nonsuperimposable mirror images. It is well known that many molecules are also chiral; examples include carbohydrates, amino acids and the peptides built from them, and DNA. Furthermore, all naturally occurring chiral molecules, with a few exceptions, exist almost exclusively in only one "handedness" (as a single so-called enantiomer). This means, in turn, that all biological systems are built from molecules of a single handedness.

The implications of this are manifold and extraordinary. For example, if I make a pharmaceutical molecule that can exist in two enantiomeric forms, each of these will be considered by your body to be totally different and may exhibit dramatically different biological properties. Pharmaceutical compounds therefore need to be made in one enantiomerically pure form. As simple as it sounds, this can be very difficult to achieve. If we are lucky, the desired target may be prepared from a convenient known and available starting material. However, such compounds (certain amino acids, carbohydrates, etc.) are relatively small in number and/or rather rare and expensive. Although enantiomers can in some cases be separated, this often requires a lot of time and energy, and up to 50% of the starting material ends up as waste. On page 642 of this issue, Bell *et al.* (*1*) report a major breakthrough in creating catalysts for asymmetric chemistry.

In response to these challenges, researchers have for many years worked to develop new synthetic catalysts for the synthesis of enantiomerically pure products. However, a good deal is asked of asymmetric catalysts. They must recognize their substrates, accelerate the target reaction, control the enantioselectivity, and then release their products in order to reenter the catalytic cycle. In a sense, we can really think of these catalysts as molecular robots—a term coined by Corey for oxazaborolidines in the 1980s, well before the days of nanotechnology (*2*).

Since the early days of this field, enormous progress has been made in reduction, oxidation, and isomerization reactions. Certain catalytic asymmetric reactions are now used on large industrial scales to make ton quantities of important target molecules for which no other practical method is available. In 2001, Sharpless, Knowles, and Noyori shared the Nobel Prize for their out-



Simplified synthesis. Classes of alkene substrate for asymmetric hydrogenation. MLn, meta-ligand complex; Ph, phenyl; Pro, alkene.

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standing contributions to the development of methods for the asymmetric catalysis of organic reactions (*3*). The report by Bell *et al.* (*1*) is concerned with hydrogenation of C=C bonds (i.e., alkenes, or to use their older name, olefins) by gaseous hydrogen. A quick perusal of the literature may lead one to the mistaken conclusion that this is a solved problem, as the number of reported catalysts now runs into the thousands. Almost all of these contain a metal center surrounded by an enantiomerically pure environment, created by one or more chelating ligands, that effectively controls the handedness of the product.

However, a closer reading of the literature reveals a more complex reality. For example, alkenes containing nearby coordinating functional groups such as amides (as in **1** in the figure), esters, carboxylic acids, etc., would today be regarded as relatively easy substrates. An alkene flanked by an aryl group (for example, **2**) represents a more challenging substrate, although a number of practical hydrogenation catalysts do exist for these substrates. In contrast, unfunctionalized alkenes (*4*), in which the alkene is flanked by only hydrocarbon groups (as in **3**), would be regarded as highly challenging. Indeed, until the report of Bell *et al*. (*1*), no practical method for their hydrogenation had been reported at all. (The lack of methods should not suggest that such substrates are uninteresting, and indeed the opposite is true; the products of reduction of unfunctionalized alkenes are numerous and include many target molecules of biological and medicinal importance.)

So why are some substrates relatively easy to reduce and others rather more challenging? Consider alkene **1**, which contains a coordinating group that can bind to the metal atom in the catalyst. The difference in structure between the possible diastereoisomers formed upon alkene coordination to the metal leads to a difference in their energies, and hence to a pathway for an asymmetric reduction through subsequent transfer of hydrogen to the alkene face that is attached to the metal.

In the case of **2**, the same principle applies; that is, the aromatic ring at one position provides a means for the discrimination between alkene faces, although the interactions involved (π-π stacking, etc.) are rather weaker and more subtle than for **1**. However, for the most challenging substrate **3**, there is no functional group in position to guide the catalyst in differentiating between the faces.

The Pfaltz group has long been recognized for its expertise in enantioselective hydrogenation. Catalysts developed by this research group have evolved toward ever more challenging substrate classes. Some years ago, researchers in the group found that iridium complexes of certain bidentate ligands containing a combination of phosphorus- and nitrogen-based donor groups were very effective at the asymmetric reduction of aryl-substituted alkenes such as **2** (*5*, *6*). These new catalysts opened up a whole new area of practical asymmetric hydrogenation technology, but their extension to the unfunctionalized **3** had remained elusive until now.

In the latest generation of catalysts, iridium complexes of ligand **4a** have been found to give consistently excellent results in the reduction of challenging unfunctionalized substrates such as **3**. In several cases the enantiomeric product ratio is as high as 99:1, whereas for **3** itself the reduction gives a 96:4 ratio of enantiomers, the highest selectivities for this application to date. However, the crowning triumph of the new system is its application to an extraordinary and unprecedented triple alkene reduction of substrate **5** (in one step) to give a product **6** with formation of two new chiral centers in almost total selectivity for a single enantiomeric product, the precursor of vitamin E. In this particular case, the optimal ligand proved to be **4b**, a slight variation on prototype **4a**. The authors did, of course, prove that the stereocontrol does not come from the preexisting chiral center on the substrate. This process hugely simplifies the stereoselective synthesis of an important and structurally complex series of target molecules.

The work of Bell *et al*. may represent the opening of a new chapter in asymmetric hydrogenation (*1*). It demonstrates how synthetic catalysts can be developed and modified to be successful with even the most challenging of substrates. Moreover, the report serves as an example of what a focused and dedicated group of researchers looking deeply into a specific field can achieve.

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10.1126/science.1123178

EPIDEMIOLOGY

Understanding HIV Epidemic Trends in Africa

Richard Hayes and Helen Weiss

HIV infection rates have fallen in parts of Africa, a result of decreases in risky sexual behavior. To avoid a resurgence of AIDS in these areas, HIV prevention efforts need to be sustained.

Almost 5 million individuals were newly infected with HIV during 2005, more than in any previous year. Sub-Saharan Africa continues to bear the brunt of the pandemic and is home to more than 25 million adults and children living with HIV/AIDS, many of whom live in southern Africa where prevalence rates are extremely high. Given this grim scenario, the significant decline in HIV prevalence in Zimbabwe reported by Gregson and colleagues on page 664 of this issue (*1*)—the first clear evidence of a reduction in HIV prevalence associated with behavior change in this region of Africa—is welcome news. This is especially so, given the predicted cost-effectiveness of expanding HIV prevention programs reported by Stover *et al.* in this week's *Science* Express (*2*).

Enhanced online at www.sciencemag.org/cgi/content/full/311/5761/620

By repeated sampling of a rural population in Zimbabwe between 1998 and 2003, Gregson *et al*. show a modest decrease in overall adult HIV prevalence (from 23.0% to 20.5%), with steeper reductions of 23% and 49% in young men and women (ages 17 to 29 for young men and 15 to 24 for young women). Similar trends have been seen in recent local and national surveillance data from antenatal clinics in Zimbabwe. A major strength of the study is that it has a relatively high coverage rate and is based on population surveys. It is thus less susceptible to bias than the more widely available sentinel surveillance data of trends in HIV prevalence among antenatal clinic attendees. One particular concern may be the high rates of migration within Zimbabwe as the result of the land-resettlement schemes. Immigrants to the study area had lower HIV prevalence than long-term residents, possibly contributing to the observed reductions in HIV prevalence. However, substantial decreases in prevalence were seen even when the analysis was restricted to longer term residents, and so this finding appears to be robust.

Gregson *et al*. attribute the reduced HIV prevalence to changes in sexual behavior, citing a delay in sexual debut, a reduction in the reported number of casual sexual partners in both sexes, and a reduction in reported unpro-

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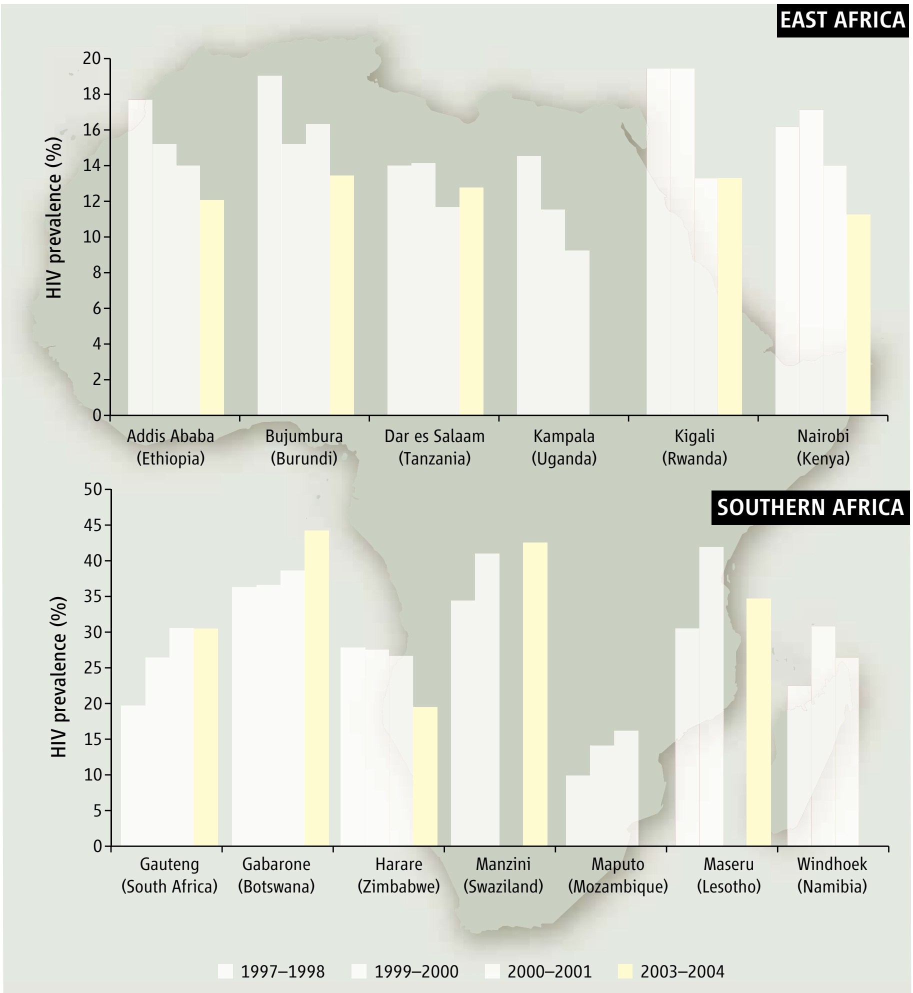
tected sex among females. As stated by the authors, the degree of behavior change has likely been overestimated because respondents may underreport their participation in socially undesirable behaviors. Nevertheless, the data suggest that changes in sexual behavior patterns are now being reflected in a decline in HIV prevalence.

Zimbabwe can now be added to the short list of countries that have seen substantial decreases in HIV prevalence. These include Uganda (*3*, *4*) and Thailand (*5*), where comprehensive and intense HIV prevention programs were followed by documented changes in reported sexual behavior, and a subsequent decline in HIV incidence and prevalence. There is also growing evidence of declining prevalence in Kenya, Burkina Faso, Cambodia, and Haiti (*6*). However, the overall picture in sub-Saharan Africa is one in which most countries now have "stable" epidemics, where AIDS-related mortality is matched by the rate of new infections, and in some southern African countries, the prevalence of HIV continues to increase (*6*) (see the figure).

The explanations for these dramatic variations lie in the transmission dynamics of this sexually transmitted infection. A useful framework for analyzing these variations is provided by the equation $R_0 = \beta cD$ (*7*), which shows how the basic reproduction number R_0 (the number of secondary infections resulting from one initial infection in a totally susceptible population) is influenced by β (the probability of sexual transmission from one infected person to an uninfected partner), *c* (a measure of the rate of sexual partner change), and *D* (the duration of infection).

Epidemiological evidence suggests that differences in both transmission probability (β) and sexual behavior (*c*) are important in explaining epidemic variations in different parts of Africa. The Four Cities study (*8*), in which comparable data on factors affecting β and *c* were collected systematically from four cities in West, East, and southern Africa, suggested that differences in transmission probability (β) were more important than differences in sexual behavior (*c*) in explaining the epidemics. That study suggested that high rates of male circumcision in West Africa may have reduced the rate of spread of HIV and other sexually transmitted infections, whereas ulcerative sexually transmitted infections (especially genital herpes) seemed more common in the high-prevalence cities of East and southern Africa. Randomized controlled trials to assess the effects of male circumcision and herpes treatment on HIV incidence and transmission are ongoing and may lead to effective interventions. Indeed, the results of the first male circumcision trial in South Africa have shown a strongly protective effect on HIV incidence (*9*). In addition to these biological factors, it is clear that behavioral characteristics are also important in defining the sexual networks through which the virus can be propagated. It is likely that the very rapid and extensive spread of HIV in many parts of southern Africa has been strongly influenced by socioeconomic factors such as the high rate of work migration. Furthermore, the falling HIV rates in Uganda, and now in Zimbabwe, seem to have been caused mainly by reductions in risky behavior.



HIV prevalence in Africa. Trends in median HIV prevalence among pregnant women, aged 15 to 49 years, who attended antenatal clinics in selected cities in East and southern Africa. [Adapted from (*6*)]

HIV incidence and prevalence remain extremely high in many countries and, despite the evidence that HIV incidence may now be declining in some parts of southern and East Africa, HIV prevention must remain a key priority for international public health. There is growing concern that, even in countries where HIV prevalence has declined, risky patterns of sexual behavior may be increasing again, and there is an urgent need to revitalize prevention efforts to avoid resurgences of the epidemic (*4*, *6*). Another reason why HIV prevention needs to be sustained and intensified is that access to antiretroviral therapy is becoming more widespread, bringing much needed relief to the large numbers of patients with advanced HIV infection. The intended effect of widening access to treatment is, of course, to extend the lives of HIV-infected subjects. Unless the incidence of new infections can be brought under control, the consequence will be a further increase in HIV prevalence and in the numbers needing antiretroviral therapy in the future. Further, investment now in scaling up HIV prevention programs has been shown to produce net savings in costs of treatment and care in the future (*2*). HIV prevention is thus more, and not less, important than ever before.

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10.1126/science.1124072

Toxic Potential of Materials at the Nanolevel

Andre Nel,[1,2]* Tian Xia,[1] Lutz Mädler,[3] Ning Li[1]

Nanomaterials are engineered structures with at least one dimension of 100 nanometers or less. These materials are increasingly being used for commercial purposes such as fillers, opacifiers, catalysts, semiconductors, cosmetics, microelectronics, and drug carriers. Materials in this size range may approach the length scale at which some specific physical or chemical interactions with their environment can occur. As a result, their properties differ substantially from those bulk materials of the same composition, allowing them to perform exceptional feats of conductivity, reactivity, and optical sensitivity. Possible undesirable results of these capabilities are harmful interactions with biological systems and the environment, with the potential to generate toxicity. The establishment of principles and test procedures to ensure safe manufacture and use of nanomaterials in the marketplace is urgently required and achievable.

By some estimates, nanotechnology promises to far exceed the impact of the Industrial Revolution and is projected to become a $1 trillion market by 2015. Engineered nanomaterials (NM) are already being used in sporting goods, tires, stain-resistant clothing, sunscreens, cosmetics, and electronics and will also be increasingly utilized in medicine for purposes of diagnosis, imaging, and drug delivery. Mihail Roco of the U.S. National Nanotechnology Institute envisages four generations of nanotechnology. The current era is that of passive nanostructures, materials designed to perform one task. The second phase will introduce active nanostructures for multitasking, for example, actuators, drug delivery devices, and sensors. The third generation is expected to emerge around 2010 and feature nanosystems with thousands of interacting components. A few years after that, the first integrated nanosystems, functioning much like a mammalian cell with hierarchical systems within systems, are expected to evolve.

The unusual physicochemical properties of engineered NM are attributable to their small size (surface area and size distribution), chemical composition (purity, crystallinity, electronic properties, etc.), surface structure (surface reactivity, surface groups, inorganic or organic coatings, etc.), solubility, shape, and aggregation. Although impressive from a physicochemical viewpoint, the novel properties of NM raise concerns about adverse effects on biological systems, which at the cellular level include structural arrangements that resemble NM in terms of their function. Indeed, some studies suggest that NM are not inherently benign and that they affect biological behaviors at the cellular, subcellular, and protein levels (*1*–*5*). Moreover, some nanoparticles readily travel throughout the body, deposit in target organs, penetrate cell membranes, lodge in mitochondria, and may trigger injurious responses.

There is almost unanimous opinion among proponents and skeptics alike that the full potential of nanotechnology requires attention to safety issues. Already there are outcries from environmental activists calling for a worldwide moratorium on NM research and marketing until protocols are in place to ensure worker safety. Science fiction novels and news media reports have also perpetuated a scary scenario in which self-replicating nanoscale robots consume all available materials, ultimately strangling the planet in a "gray goo." Although this scenario is implausible from an energy as well as a structural assembly viewpoint, it points to the need to develop a rational, science-based approach to nanotoxicology. It is our opinion that such an approach is feasible and should be implemented to ensure the safe manufacturing and marketing of engineered nanoproducts.

Do Nanomaterials Properties Necessitate a New Toxicological Science?

The main characteristic of NM is their size, which falls in the transitional zone between individual atoms or molecules and the corresponding bulk materials. This can modify the physicochemical properties of the material as well as create the opportunity for increased uptake and interaction with biological tissues. This combination of effects can generate adverse biological effects in living cells that would not otherwise be possible with the same material in larger form. Although the extraordinary properties of NM may necessitate a novel investigative approach to assess their hazard potential, particle toxicology is a mature science that addresses the mechanisms of lung injury by inhaled particles (*4*–*6*). Inhaled or instilled ambient ultrafine particles (particulate matter with an aerodynamic diameter < 100 nm) can induce pulmonary inflammation, oxidative stress, and distal organ involvement. In a similar fashion, occupational exposure to quartz, mineral dust particles (e.g., coal and silicates), and asbestos fibers induce oxidative injury, inflammation, fibrosis, cytotoxicity, and mediator release from lung target cells (*4*–*8*). The same holds true for experimental instillation of titanium dioxide (TiO_2) and carbon black nanoparticles in animal lungs. Tissue and cell culture analysis support the physiological response seen in animal models, pointing to the role of oxidative stress in the production of inflammatory cytokines and cytotoxic cellular responses. Taken together, these clinical and experimental studies indicate that a small size, a large surface area, and an ability to generate reactive oxygen species (ROS) play a role in the ability of nanoparticles to induce lung injury (*4*–*8*). Thus, as the particle size shrinks, there is a tendency for pulmonary toxicity to increase, even if the same material is relatively inert in bulkier form (e.g., carbon black and TiO_2). However, particle coating, surface treatments, surface excitation by ultraviolet (UV) radiation, and particle aggregation can modify the effects of particle size. It is possible, therefore, that some nanoparticles may exert their toxic effects as aggregates or through the release of toxic chemicals.

Particle size and surface area are important material characteristics from a toxicological perspective. As the size of a particle decreases, its surface area increases and also allows a greater proportion of its atoms or molecules to be displayed on the surface rather than the interior of the material. Figure 1 shows the inverse relationship between the particle size and the number of molecules expressed on the particle surface. Table 1 shows that, as the particle size for a group of airborne particles with fixed mass (10 $\mu g/m^3$) and unitary density (1 g/cm^3) decreases, their number increases exponentially along with the surface area. The increase in surface area determines the potential number of reactive groups on the particle surface.

The change in the physicochemical and structural properties of engineered NM with a decrease in size could be responsible for a number of material interactions that could lead to toxicological effects (*4*, *7*). For instance, shrinkage in size may create discontinuous crystal planes that increase the number of structural defects as well as disrupt the well-structured electronic configuration of the material, so as to give rise to altered electronic

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properties (Fig. 2) (*4*, *7*). This could establish specific surface groups that could function as reactive sites (Fig. 2). The extent of these changes and their importance strongly depend on the chemical composition of the material. Surface groups can make NM hydrophilic or hydrophobic, lipophilic or lipophobic, or catalytically active or passive (Fig. 2). An example of how those surface properties can lead to toxicity is the interaction of electron donor or acceptor active sites (chemically or physically activated) with molecular dioxygen (O_2). Electron capture can lead to the formation of the superoxide radical ($O_2^{\cdot-}$), which through dismutation or Fenton chemistry can generate additional ROS. Single-component materials as well the presence of transition metals on the surface can participate in the formation of such active sites. For instance, ultrafine particles contain transition metals (e.g., Fe and vanadium) and are also coated with redox-cycling organic chemicals (e.g., quinones), whereas carbon nanotubes contain metal impurities that can amplify chemical changes in the NM environment (Fig. 2). Thus, several NM characteristics can culminate in ROS generation (*9*), which is currently the best-developed paradigm for nanoparticle toxicity (Table 2). Other NM properties such as shape, aggregation, surface coating, and solubility may also affect the addressed specific physicochemical and transport properties, with the possibility of negating or amplifying the size effects (Fig. 2).

The Biology of Particle-Induced Oxidative Stress as an Important Mechanistic Paradigm on Which to Base a Predictive Model for Studying NM Toxicity

There is a direct relationship between the surface area, ROS-generating capability, and pro-inflammatory effects of nanoparticles in the lung (*4*–*8*). From a mechanistic perspective, ROS generation and oxidative stress is the best-developed paradigm to explain the toxic effects of inhaled nanoparticles (*3*–*10*). Under normal coupling conditions in the mitochondrion, ROS are generated at low frequency and are easily neutralized by antioxidant defenses such as glutathione (GSH) and antioxidant enzymes (*11*). However, under conditions of excess ROS production, such as may occur in the lung and possibly the circulatory system during ambient or occupational nanoparticle exposures (*8*), the natural antioxidant defenses may be overwhelmed (*11*). Oxidative stress refers to a state in which GSH is depleted while oxidized glutathione (GSSG) accumulates (*11*). Cells respond to this drop in the GSH/GSSG ratio by mounting protective or injurious responses (*8*, *10*–*12*). The oxidative stress resulting from real-life ambient and occupational particle exposures, as well as experimental challenge with ambient particulate matter (PM), quartz, carbon black, or TiO_2 nanoparticles, results in airway inflammation and interstitial fibrosis (*3*–*8*).

Mechanistic studies that use discovery tools such as proteomics and genomics have proven useful for substantiating mechanistic hypotheses (*12*) explaining the biology of oxidative stress, and developing biomarkers. According to the hierarchical oxidative stress hypothesis, the lowest level of oxidative stress is associated with the induction of antioxidant and detoxification enzymes (Fig. 3) (*12*). The genes that encode the phase II enzymes are under the control of the transcription factor Nrf-2. Nrf-2 activates the promoters of phase II genes via an antioxidant response element (ARE) (*12*). Defects or aberrancy of this protective response pathway may determine disease susceptibility during ambient particle exposure. At higher levels of oxidative stress, this protective response is overtaken by inflammation and cytotoxicity (Fig. 3). Inflammation is initiated through the activation of pro-inflammatory signaling cascades [e.g., mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB) cascades], whereas programmed cell death could result from mitochondrial perturbation and the release of pro-apoptotic factors (Fig. 3). It is noteworthy that several different types of nanoparticles, including ambient ultrafines, target mitochondria directly (*4*, *12*).

A number of responses at each level of oxidative stress have now been successfully incorporated as screening assays for toxicological effects of ambient PM in vivo, for example, increased expression of antioxidant enzymes and cytokines in the lungs of exposed animals. Moreover, knockout or genetic polymorphisms of genes that encode for phase II enzymes establish a susceptibilty mechanism that may determine why only some individuals develop PM-induced injury (*13*). Characterization of particle size and physical characteristics, together with in vitro assays for ROS and oxidative stress (phase II responses, inflammation, and mitochodrion-mediated apoptosis) plus in vivo markers of oxidative stress (e.g., lipid peroxidation and signature cytokines), is an example of a predictive paradigm for toxicity screening. Similar paradigms can be developed for engineered NM. These assays can be supplemented with nanosensor systems that are designed to interrogate the abilities of NM to generate ROS.

In addition to the paradigm of oxidative stress and inflammation, it is important to consider that some of the NM interactions depicted in Fig. 2 may also results in other forms of injury, such as protein denaturation, membrane damage, DNA damage, immune reactivity, and the formation of foreign body granulomas (Table 2). It is also possible that new NM properties may emerge that can lead to novel mechanisms of toxicity.

Are Occupational and Inhalation Exposures to Ambient Nanoparticles Applicable to Engineered NM?

Uses of engineered NM in sunscreens [e.g., TiO_2 and zinc oxide (ZnO)] and cosmetics and as bioimaging probes (e.g., superparamagnetic iron oxides) have not lead to reports of clinical toxicity in humans. However, although inhalation of ultrafine ZnO particles at relatively high dose (500 μg/m^3) for 2 hours did not induce acute systemic effects in humans, inhalation of ZnO fumes in an occupational setting can cause metal fume fever (fatigue, chills, fever, myalgias, cough, dyspnea, leukocytosis, metallic taste, and salivation) (*14*). Only a limited number of NM have so far been shown to exert toxicity in tissue culture and animal experiments, usually at high doses (*2*, *4*). For instance, intratracheal instillation of TiO_2 particles in rodents demonstrates that these nanoparticles induce bigger inflammatory responses than larger particles of an equivalent mass dose (*4*). However, when the instilled dose is expressed as particle surface area, the inflammatory response fits the same dose-response curve (*3*–*7*). This supports the concept that the surface area is the dose measurement that best predicts pulmonary toxicity (*4*–*8*). In addition to the generation of pro-inflammatory effects, nanoparticles of various sizes and chemical composition are able to lodge in mitochondria (*4*, *15*). This can lead to disruption of the mitochondrial electron transduction chain, which leads to additional $O_2^{\cdot-}$ production (*15*). Further, ambient ultrafine particles perturb the mitochondrial permeability transition pore, which leads to the release of pro-apoptotic factors and programmed cell death (*15*).

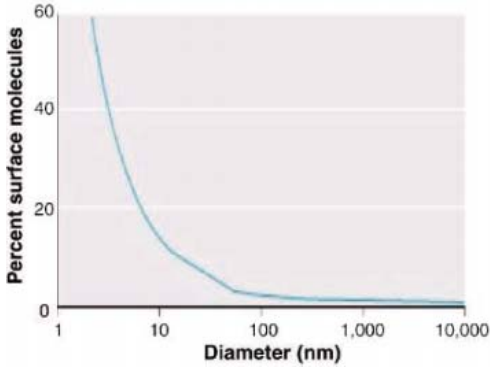

Fig. 1. Inverse relationship between particle size and number of surface expressed molecules. In the size range < 100 nm, the number of surface molecules (expressed as a % of the molecules in the particle) is inversely related to particle size. For instance, in a particle of 30 nm size, about 10% of its molecules are expressed on the surface, whereas at 10 and 3 nm size the ratios increase to 20% and 50%, respectively. Because the number of atoms or molecules on the surface of the particle may determine the material reactivity, this is key to defining the chemical and biological properties of nanoparticles. [Adapted from (*4*)]

In addition to the above materials, carbon nanostructures are one of the limited types of engineered nanostructures that have undergone some toxicity testing (*2*, *4*). This includes testing of fullerenes, which in their basal state are composed of 60 carbon atoms (C60) in the shape of a sphere. Fullerenes have many potential applications based on their unique free radical chemistry and antioxidant properties. Specific surface treatments are required to disperse the fullerenes in suspensions for in vitro and in vivo testing (*2*). Their ability to induce toxicity may also require a light or ultraviolet (UV) source to excite the fullerene surface (*2*) (Fig. 2). Water-soluble, monodisperse, or colloidal fullerene aggregates induce $O_2^{\cdot-}$ anions, lipid peroxidation, as well as cytotoxicity. On the other hand, modification of the fullerene surface by attachment of malonyl groups yields nanoparticles with biologically useful antioxidant activity (*16*). Even at high doses, animal studies have demonstrated minimal dermal and oral toxicity (*2*). Fullerenes have to be systemically administered at relatively high dose to achieve acute toxicity; the median lethal dose for a water-soluble fullerene was 600 mg/kg (*17*). Although the exposure of largemouth bass to fullerenes leads to lipid peroxidation in the brain and glutathione depletion in their gills, it is unclear why these biological effects disappeared at higher concentrations (*18*).

Carbon nanotubes are long carbon-based tubes that can be either single- or multiwalled and have the potential to act as biopersistent fibers. Nanotubes have aspect ratios ≥ 100, with lengths of several μm and diameters of 0.7 to 1.5 nm for single-walled nanotubes (SWNT) and 2 to 50 nm for multiwalled nanotubes (MWNT). In vitro incubation of keratinocytes and bronchial epithelial cells with high doses of SWNT results in ROS generation, lipid peroxidation, oxidative stress, mitochondrial dysfunction, and changes in cell morphology (*19*). MWNT also elicit proinflammatory effects in keratinocytes (*20*). Several studies using intratracheal instillation of high doses of nanotubes in rodents demonstrated chronic lung inflammation, including foreign-body granuloma formation and interstitial fibrosis (*9*, *21*, *22*). These studies also reveal the tendency of the nonphysiologic administration route and the unrealistic high doses to lead to asphyxiation through nanotube clumping in the airways (*21*). Although it has been suggested that the granulomatous inflammation could be a biopersistent fiber effect, similar to the effect of asbestos fibers, the high dose of the aggregated nanotubes and the presence of metal impurities (e.g., Fe) could account for artificial toxicity. There is also a question of whether the manufacture of nanotubes under closed gas-phase conditions will lead to substantial inhalation exposure of factory workers. It is possible that the release of nanotubes from an intended commercial use product such as car tires could become airborne.

Table 1. Particle number and particle surface area for 10 μg/m³ airborne particles (*5*).

Particle diameter (μm)	Particles/ml of air	Particle surface area (μm²/ml of air)
2	2	30
0.5	153	120
0.02	2,390,000	3000

All considered, the limited toxicity data for engineered NM confirm that ROS production may play a role under some experimental conditions (e.g., light or UV exposure) or when these materials contain metal impurities. Although at high dose the generation of ROS and oxidative stress could lead to NM toxicity, it is not clear that these experimental findings are directly related to clinical toxicity. This differs from the data on ambient ultrafine particles. Ultrafine particles are mostly derived from combustion sources, are heterogeneous in size, exist in single or aggregated form, and have a chemical structure consisting of a solid core made of either inorganic material (sulfuric acid and transition metals) or soot surrounded by a layer of adsorbed or condensed semi-volatile organic constituents, all of which can contribute to ROS generation (*23*). This is quite different from the homogeneous composition and size of engineered NM that occasionally contain transition metals. Even though these differences led some experts to question the relevance of ambient nanoparticle research to the study of NM, it is important to recognize that PM research has established important principles of particle toxicity that may be applicable to NM. This includes the recognition that small particle size, chemical composition, and the presence of a large reactive surface area can catalyze ROS production.

What Are the Biological and Biokinetic Properties of NM that Need to Be Considered for Toxicity Testing?

The biological impacts of NM and the biokinetics of nanoparticles are dependent on size, chemical composition, surface structure, solubility, shape, and aggregation. These parameters can modify cellular uptake, protein binding, translocation from portal of entry to the target site, and the possibility of causing tissue injury (*4*). At the target site, NM may trigger tissue injury by one or more mechanisms (Table 2). Potential routes of NM exposure include gastrointestinal tract (GIT), skin, lung, and systemic administration for diagnostic and therapeutic purposes. NM interactions with cells, body fluids, and proteins play a role in their biological effects and ability to distribute throughout the body. NM binding to proteins may generate complexes that are more mobile and can enter tissue sites that are normally inaccessible. Accelerated protein denaturation or degradation on the nanoparticle surface may lead to functional and structural changes, including interference in enzyme function (*24*). This damage could result from splitting of intramolecular or intramolecular

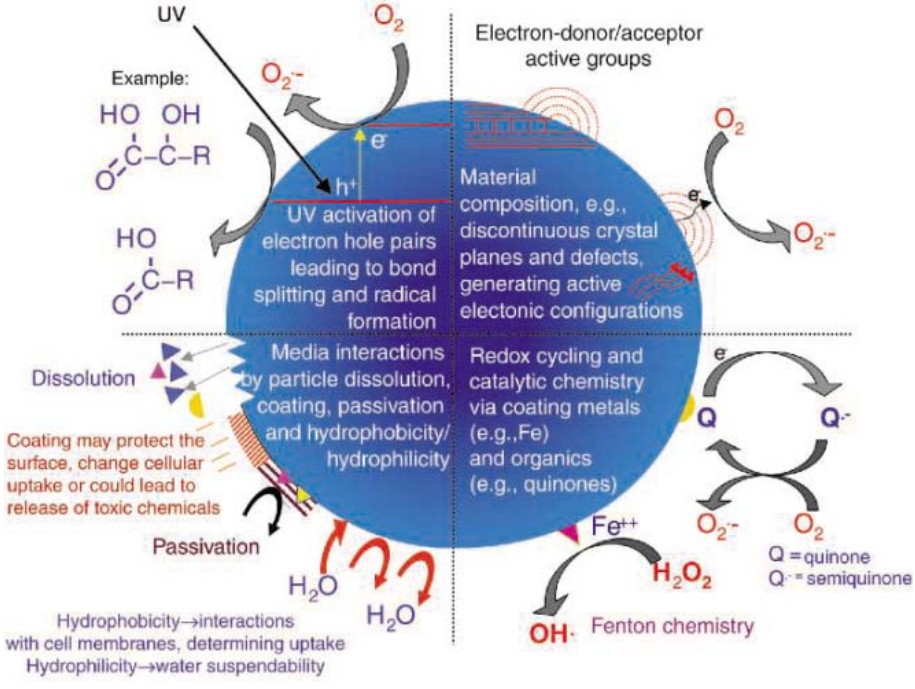

Fig. 2. Possible mechanisms by which nanomaterials interact with biological tissue. Examples illustrate the importance of material composition, electronic structure, bonded surface species (e.g., metal-containing), surface coatings (active or passive), and solubility, including the contribution of surface species and coatings and interactions with other environmental factors (e.g., UV activation).

bonds by catalytic chemistry on the material surface (Fig. 2). Throughout their uptake and transport through the body, NM will encounter a number of defenses that can eliminate, sequester, or dissolve nanoparticles. In addition, cells and tissues have effective antioxidant defenses that deal with ROS generation (Fig. 3).

Although inhalation is a less likely route for engineered NM exposure compared with ambient or mineral dust particles, this can happen during bulk manufacture and handling of freely dispersable nanoparticles. Inhaled nanoparticles are efficiently deposited by diffusional mechanisms in all regions of the lung (*4*). Several defense mechanisms, including mucociliary escalator transport and phagocytosis by macrophages, keep the mucosal surfaces free from deposited particles. It has been proposed that Radio-labeled ultrafine carbon black may translocate through the respiratory epithelial layer to reach the lung interstitium or the blood and lymph circulations, but this finding has been refuted by others (*25*, *26*). Theoretically this could involve alveolo-capillary translocation via endocytosis, transcytosis, or unidentified cellular mechanisms (*27*). In nonphagocytic cells, these endocytic events are regulated by clathrin-coated pits and caveolae, as well as scavenger receptors (e.g., scavenger receptor SR-A) (*27*, *28*). Caveolae are indentations of the plasma membrane decorated with caveolin-1 and are abundantly expressed on lung capillaries and type l alveolar cells. It has been hypothesized that inspiratory expansion and expiratory contraction of lung alveoli may lead to the opening and closing of the caveolae to assist macromolecular transport across the alveolar membrane (*29*). Although it has been suggested that caveolae and coated pits preferentially transport small and large particles, respectively, it is unclear whether this specificity exists in vivo (*27*). Surface coating of nanoparticles also needs to be considered in particle uptake. Albumin, lecithin, polyethylene glycol, polysorbital 80 or peptide attachments can enhance nanoparticle uptake into cells, whereas polyethylene glycol interferes in nanoparticle uptake in the liver (*30*). Particle coating may be of particular importance in the lung, where adsorbtion of epithelial lining fluid components and surfactant can influence particle interactions with epithelial cells (Fig. 2). Similarly, the state of particle aggregation or dispersion is important in cellular interactions as exemplified by the finding that, if nanoparticles are coated with lung surfactant before cellular incubation, the cellular fate differs from that of uncoated particles. The assessment of nanomaterial inorganic and organic coatings and state of aggregation are therefore important considerations in evaluating NM toxicity.

Animal and human studies suggest that alveolar translocation of nanoparticles leads to circulatory access and allows nanoparticles to distribute themselves throughout the body, including the vasculature, heart, liver, spleen, and bone marrow. However, the extent of extrapulmonary translocation is highly variable and depends on particle size, surface characteristics, and chemical composition. Particle access to the blood circulation and effects on the endothelium and vasculature could explain why exposure to ambient ultrafine particles has been associated with cardiovascular events such as heart attacks and cardiac rhythm disturbances (*8*, *25*, *31*).

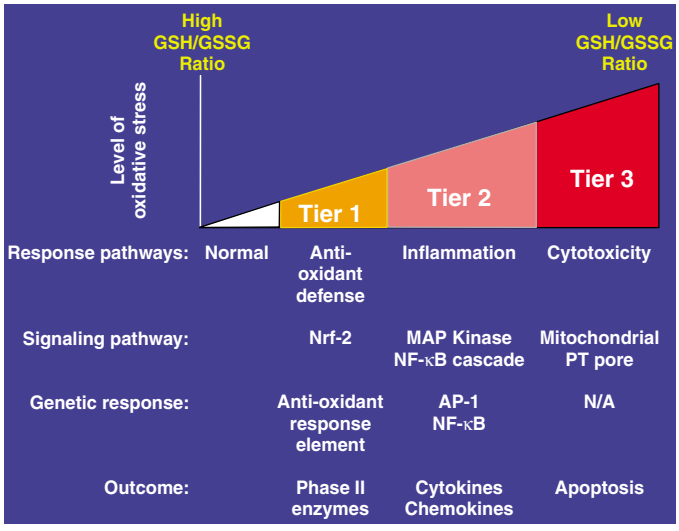

Fig. 3. The hierarchical oxidative stress model. At a lower amount of oxidative stress (tier 1), phase II antioxidant enzymes are induced via transcriptional activation of the antioxidant response element by Nrf-2 to restore cellular redox homeostasis. At an intermediate amount of oxidative stress (tier 2), activation of the MAPK and NF-κB cascades induces pro-inflammatory responses. At a high amount of oxidative stress (tier 3), perturbation of the mitochondrial PT pore and disruption of electron transfer results in cellular apoptosis or necrosis. [Adapted from (*11*)] N/A means not applicable.

Dermal exposure to NM occurs regularly during the use of sunscreen products, for example, TiO_2 and ZnO nanoparticles, that are often coated for minimizing their reactivity while maintaining their UV absorption properties. In healthy skin, the epidermis provides excellent protection against particle spread to the dermis. However, flexing of normal skin facilitates the penetration of micrometer-size fluorescent beads to the dermis (*32*). Damaged skin also allows micrometer-size particles access to the dermis and regional lymph nodes. In vivo imaging using intradermally injected quantum dots has been used to confirm particle trafficking to regional lymph nodes in animals (*33*). Such trafficking could deliver the particles to paracortical areas in the lymph nodes where macrophages and dendritic cells (DC) specialize in the uptake of particulate matter. This could lead to effects on the immune system.

The likelihood of immune perturbation by nanoproducts is unknown. Although the reticuloendothelial system, which is composed of phagocytic cells in the liver, spleen, and lymph nodes, clears or sequesters nanoparticles, self-protein interactions with particles may change their antigenicity and initiate autoimmune responses. Nanoparticle-protein complexes are also more mobile and may facilitate antigen uptake by DC. This can lead to boosting of primary and secondary immune responses by changing the antigen presentation function of DC. For instance, diesel exhaust and other ambient particles act as adjuvants that, through their impact on DC function, lead to an exaggerated immune response to common environmental allergens (*34*). Lastly, there is the possibility that the immune system directly recognizes NM, as exemplified by the antibody response to C60 in mice injected with albumin-conjugated fullerenes (*35*).

NM can be ingested directly in food, water, cosmetics, or drugs. Alternatively, nanoparticles cleared via the mucociliary escalator in the respiratory tract can end up in the GIT. Although nanoparticles in food are infrequently taken up into gut lymphatics and distributed to other organs, most nanoparticles are rapidly eliminated via feces. For instance, radioactive iridium nanoparticles do not show substantial GIT uptake, whereas ingestion of water-soluble radiolabeled C60 fullerenes in rats show a 98% clearance in the feces (*36*, *37*). In contrast, 90% of intravenously administered radio-labeled fullerenes are retained for at least a week, with >70% lodging in the liver.

The potential for nanoparticle translocation to the brain via olfactory nerve endings in the nose has recently been reported (*38*). The close proximity of the nasal olfactory mucosa to the olfactory bulb may facilitate neuronal uptake. Earlier studies showed that the olfactory nerve and olfactory bulb are indeed portals of entry into the primate brain by viral or metal nanoparticles instilled in the nose. Whether nanoparticles in the brain have any pathological or clinical significance is uncertain.

Although no clinically relevant toxicity has yet been reported, it is too early to draw meaningful conclusions about the inherent dangers of engineered NM. It remains to be determined whether the unique physicochemical properties of NM will introduce new mechanisms of injury and whether these will result in new pathology. Generally speaking, biological systems are able to integrate

multiple pathways of injury into a limited number of pathological outcomes, such as inflammation, apoptosis, necrosis, fibrosis, hypertrophy, metaplasia, and carcinogenesis (Table 2). However, even if NM do not introduce new pathology, there could be novel mechanisms of injury that require special tools, assays, and approaches to assess their toxicity (Table 2).

As NM Are Being Introduced as Commercial Products, What Should Be Done to Ensure That They Are Safe?

In contrast to the debates on nuclear power and genetically altered food, the public does not yet view nanotechnology as a noteworthy hazard. However, this position could change rapidly with media interest in this topic. Now is an opportune time to inform the public and to establish the principles and procedures that will ensure the safety of this technology for workers, consumers, and the environment. Because of the wide range of nanoproducts in use or under development, it is important to establish which materials should be tested first and how to perform this testing. NM that are near commercialization and are produced in large quantities as freely dispersible nanoparticles, with the potential of substantial exposures in humans and the environment, should probably be given preference. It is also important for regulatory agencies to develop positive and negative benchmarks that can be used as reference controls. On the basis of current understanding, the traditional study methods for testing chemical toxicity are a good starting point for NM testing. However, given the unique characteristics of NM, this will necessitate new test strategies to delineate the novel mechanisms of injury that may arise from these materials (Table 2). More refined approaches for NM characterization and toxicological evaluations will emerge with time, for example, use of nanosensors to detect ROS generation by nanoparticles. This could make these evaluations cost effective, facilitating new product development.

What type of NM testing should be performed? The National Toxicology Program (NTP) in the United States has been established as an interagency program to evaluate chemical agents that are of public health concern by implementing modern toxicology tools. [Other governmental agencies, such as the Environmental Protection Agency (EPA) and the National Institute of Occupational Safety and Health (NIOSH) also have important roles in assessing nanomaterial safety in the United States, which will not be discussed here]. Although it is still questionable whether NM should be treated as commercial or industrial chemicals, the preferred NTP approach to chemical toxicity is a predictive scientific model that focuses on target-specific, mechanism-based biological observations, rather than a descriptive approach (*39*). Briefly, this strategy makes use of existing data, if available, to attempt to classify a material at the outset as hazardous or not. If a potentially hazardous chemical is nominated for study, a specific test strategy for that chemical is developed that takes into consideration the existing data at the time of nomination. For instance, if the evidence is suggestive of pulmonary toxicity, a test strategy is used to study those effects on tissue culture cells of lung origin in vitro and in the lungs of live animals. In vitro assays allow specific biological and mechanistic pathways to be isolated and tested under controlled conditions in ways that are not feasible by using in vivo studies. Ideally, the studies are conducted in combination with in vivo studies that reveal a link of the mechanism of injury to the pathophysiological outcome in the target organ (Table 2). In vivo studies make use of animal models, including different time-length exposures (*39*).

While the same approach can work for NM testing, it is important that the design be pragmatic and mechanism-based. The demand for a predictive and pragmatic approach becomes clear when we consider that, among the 80,000 chemicals that are currently registered for commercial use in the United States, only 530 have undergone long-term and 70 short-term testing by the NTP. Moreover, the resource-intensive nature of these studies puts the cost of each bioassay at $2 to $4 million and takes over 3 years to complete. Thus, although it is optimal to collect data at different tiers of toxicity, some flexibility is required to develop decision matrixes for in vitro and in vivo testing. Ultimately, the goal of the predictive approach would be to develop a series of toxicity assays that can limit the demand for in vivo studies, both from a cost as well as an animal-use perspective. Much can be learned from research into the adverse health effects of ambient PM, where progress was slow until major mechanistic hypotheses were introduced. Armed with the knowledge that particle size, surface area, and chemical composition are important for ROS generation as a key toxicity principal, it has become easier to design in vivo studies in at-risk populations (*8*). The extent to which this or other paradigms of injury (Table 2) apply to a wide range of NM needs to be determined.

Although it is not possible to provide detailed protocols for nanotoxicity testing here, it will suffice to mention that the three key elements of a toxicity screening strategy should include physicochemical characterization of NM, in vitro assays (cellular and noncellular), and in vivo studies (*40*). There is a strong likelihood that biological activity will depend on physicochemical characteristics that are not usually considered in toxicity screening studies. Thus, any test paradigm must attempt to characterize the test material with respect to size (surface area, size distribution), chemical composition (purity, crystallinity, electronic properties, etc.), surface structure (surface reactivity, surface groups, inorganic/organic coatings, etc.), solubility, shape and aggregation. This should be done at the time of NM administration as well as at the conclusion, if possible. It is beyond the scope of this paper to discuss the scientific methods for NM character-

Table 2. NM effects as the basis for pathophysiology and toxicity. Effects supported by limited experimental evidence are marked with asterisks; effects supported by limited clinical evidence are marked with daggers.

Experimental NM effects	Possible pathophysiological outcomes
ROS generation*	Protein, DNA and membrane injury,* oxidative stress†
Oxidative stress*	Phase II enzyme induction, inflammation,† mitochondrial perturbation*
Mitochondrial perturbation*	Inner membrane damage,* permeability transition (PT) pore opening,* energy failure,* apoptosis,* apo-necrosis, cytotoxicity
Inflammation*	Tissue infiltration with inflammatory cells,† fibrosis,† granulomas,† atherogenesis,† acute phase protein expression (e.g., C-reactive protein)
Uptake by reticulo-endothelial system*	Asymptomatic sequestration and storage in liver,* spleen, lymph nodes,† possible organ enlargement and dysfunction
Protein denaturation, degradation*	Loss of enzyme activity,* auto-antigenicity
Nuclear uptake*	DNA damage, nucleoprotein clumping,* autoantigens
Uptake in neuronal tissue*	Brain and peripheral nervous system injury
Perturbation of phagocytic function,* "particle overload," mediator release*	Chronic inflammation,† fibrosis,† granulomas,† interference in clearance of infectious agents†
Endothelial dysfunction, effects on blood clotting*	Atherogenesis,* thrombosis,* stroke, myocardial infarction
Generation of neoantigens, breakdown in immune tolerance	Autoimmunity, adjuvant effects
Altered cell cycle regulation	Proliferation, cell cycle arrest, senescence
DNA damage	Mutagenesis, metaplasia, carcinogenesis

ization except to comment that standard reference materials (e.g., TiO_2, carbon black, quartz) are essential to compare material behavior. Cellular assays should reflect portal-of-entry toxicity in lungs, skin, and mucus membranes as well as noxious effects on target tissue such as endothelium, blood cell elements, spleen, liver, nervous system, heart, and kidney. Noncellular assays could include protein interactions and pro-oxidant activity. The in vivo studies can make use of disease-specific animal models that assess portal of entry and target organ injury, as well as animal models in which live imaging can be used to show the activation of oxidative stress and redox signaling pathways that are involved in particle-induced tissue injury (Fig. 3). When in vivo toxicity is observed, it may also be appropriate to proceed with studies that formerly assess the absorption, distribution, metabolism, and elimination of NM. Because NM have the potential to spread beyond the portal of entry, it is important to assess systemic responses. Examples include assays for oxidative stress (e.g., lipid peroxidation), C-reactive protein, immune and inflammatory responses, and cytotoxicity (e.g., release of liver enzymes and glial fibrillary acidic protein). The biological studies can be strengthened by the use of discovery tools such as proteomics and genomics to develop biomarkers for toxicity screening (*12*).

As testing proceeds, it will be important to incorporate these data into a knowledge base that allows investigators to classify NM as safe or possibly hazardous. Negative data should be reported to show which materials are devoid of toxic effects. This could represent the majority of NM.

Potential difficulties may be encountered in conducting in vitro and in vivo studies with engineered NM. These include problems with dosimetry, state of agglomeration (singlets versus aggregates), impact of material coating, and lack of knowledge of real-world exposures to NM. Detection methods need to be developed for exposure assessment and dosimetry calculation. Current state-of-the-art methods to detect airborne nanoparticles should enable personal monitoring devices to be developed to assess these exposures. The position is more complicated for nanoparticles that are spread via water and, even more so, via soil. Major questions also remain how to detect nanostructures in biological tissues. To evaluate exposure-dose-response relationships, it is unclear whether the NM dose should be calculated as mass concentration, number concentration, or surface area. Where possible, it is advisable to use all three parameters. In evaluating oxidative stress injury, the most appropriate dose measure appears to be surface area, which likely reflects the number of active sites at which ROS production can take place. Successful evaluation of dose-response relationships requires an understanding of NM biokinetics, as well as developing models that reconcile experimental with in vivo dose amounts.

While engineered NM clearly represent a unique class of materials with many novel and unique physicochemical properties that could impact biological systems, it is still too early to define what hazards and risks these materials may pose. For noxious chemical substances, hazard is directly related to toxicological effects in humans and the environment. For NM it is important to consider that their unique biological properties may differ from the base materials or chemical compounds from which they are manufactured. It is still being debated whether engineered NM should receive unique identifiers for toxicological and regulatory purposes. Risk assessment takes into consideration hazard as well as exposure and is accomplished through epidemiological studies and performance of exposure modeling. Risk assessment is of key importance to the insurance industry as well as the regulatory agencies that are responsible for formulating exposure and safety guidelines. It is important for law- and policymakers to keep in mind that when scientific research or new technologies raise concern, there is often the tendency to overreact with new rules and regulations. When considering regulation of engineered NM due to concerns about adverse health and environmental effects, it is recommended that the decision be based on scientific evidence of toxicity, which preferably should consider specific products or product lines and the likelihood of an exposure risk. It is recommended that lawmakers make these decisions in consultation with the evaluating scientists, regulatory agencies, academia and industry. This could involve the establishment of a special international working committee or coalition to achieve this goal.

Issues regarding safe handling of potentially toxic NM, including questions of whether personal protective equipment is effective for protection against NM exposures, have not been solved. This problem relates to the uncertainty about the real-life NM hazards and how to demonstrate that a protective measure is effective. In the absence of quantitative information, a good approach is to start with standard hygiene procedures, including gloving, protective clothing, and highly efficient respirators capable of removing nanoparticles, and to move ahead as new information becomes available. As toxicological data become available, these should be used to develop material safety data sheets that inform workers and consumers of possible NM hazards, including safe handling procedures. Other important questions relate to disposal of NM and spill remediation. Although very little is currently known about this area, it is probably wise to regard NM waste as potentially hazardous until proven otherwise.

Summary

Although it is possible that engineered NM may create toxic effects, there are currently no conclusive data or scenarios that indicate that these effects will become a major problem or that they cannot be addressed by a rational scientific approach. At the same time, we can no longer postpone safety evaluations of NM. A proactive approach is required, and the regulatory decisions should follow from there. In addition to facilitating the safe manufacture and implementation of engineered nanoproducts, an understanding of nanotoxicity could also have a positive sequel. For instance, the propensity of some nanoparticles to target mitochondria and initiate programmed cell death could be used as a new cancer chemotherapy principle.

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Effective Seed Dispersal Across a Fragmented Landscape

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Anthropogenic disturbances have fragmented native woodland, leaving tree populations susceptible to the deleterious effects of reduced gene flow. There is evidence that, in fragmented landscapes, pollen disperses over larger distances than theoretically anticipated (*1*), which could potentially offset these effects. However, despite the predominant role of seed dispersal and establishment in determining population genetic structure, contemporary gene movement has rarely been estimated after seed establishment (*2*, *3*). The dogma has been that pollen dispersal is the main vector of gene flow among fragments, whereas seed-mediated gene flow generated from rare long-distance dispersal events is primarily important for colonization. Here we show that seed dispersal is up to six times more effective than pollen dispersal at maintaining genetic connectivity among remnants of a wind-pollinated, wind-dispersed temperate tree, *Fraxinus excelsior*, across a chronically deforested landscape (*4*).

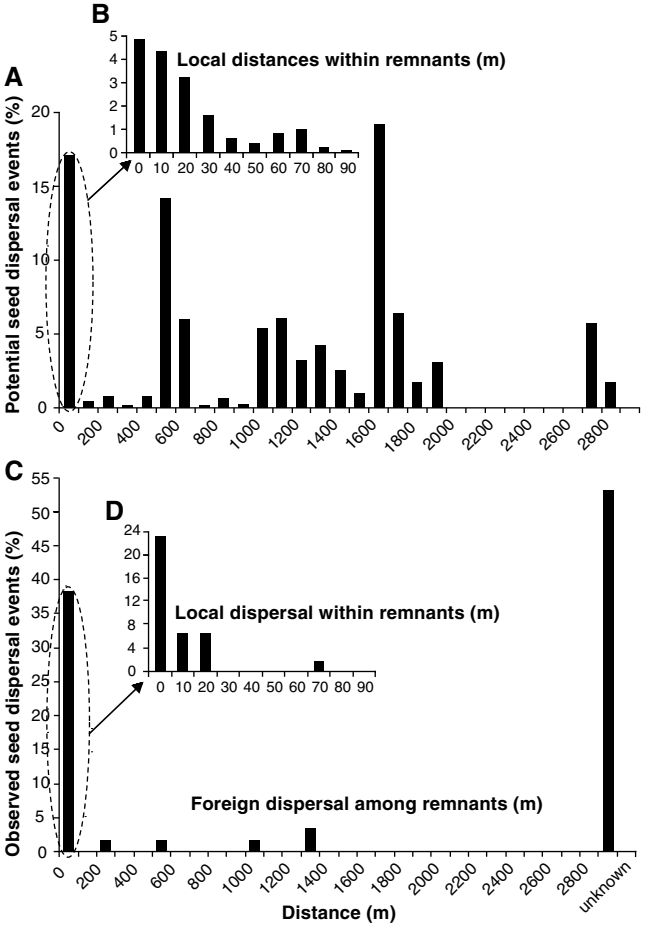

Fig. 1. Comparison of potential and observed seed dispersal within and among *F. excelsior* remnants in Moffat Dale (*4*). (**A**) Frequency distribution of the pairwise distance between the 88 trees and 60 seedlings sampled. (**B**) Close-up on the tree-seedling pairwise distance distribution within remnants (<100 m). (**C**) Frequency distribution of effective seed dispersal events within (<3000 m) and outside of Moffat Dale. (**D**) Close-up on local seed dispersal (<100 m). Effective seed dispersal events were identified by means of maximum-likelihood parentage analysis in FAMOZ (*5*). When a single parent was identified, it was assumed to be the maternal parent. When a parent pair was identified, the nearest parent was assumed to be the maternal parent.

Parentage analysis is a practical tool to meet the challenge of estimating the scale and quality of long-distance dispersal (*5*). We determined the parentage of 60 seedlings that were establishing in three focal forest remnants (*6*). We assigned parentage to either local trees or foreign trees that were located in other extant remnants within a 900-ha deforested valley in the Southern Uplands of Scotland (*4*). We found that gene flow into each remnant is extensive (67.5 to 87.5% of assignments). Furthermore, whereas only 25 to 35% of the seedlings were pollinated by foreign pollen but dispersed from local trees, 50 to 75% became established after long-distance dispersal of foreign seeds (*6*).

We recorded seed dispersal covering distances up to 1.4 km and quantified the contribution of both local and long-distance dispersal to establishment (Fig. 1). Although 38% of the seedlings were dispersed from local trees, 8% originated from trees located in one of four neighboring remnants (100 m to 3 km). Our empirical data therefore corroborate modeling predictions of a leptokurtic dispersal curve (Fig. 1) (*5*). Up to 53% of seed-mediated gene flow (and at least 46% after correction for cryptic gene flow) is estimated to occur from outside the sampled area of 900 ha. Therefore, the tail of the dispersal curve, similar to that for pollen (*4*), may spread over tens of kilometers. Secondary wind or water dispersal may contribute to such long-distance dispersal. However, modeling evidence (*5*) supports the idea that the barren landscape of the Southern Uplands increases the likelihood that such winged-seed will be uplifted and the idea that the exposed environment of deforested landscapes favors long-distance dispersal of both pollen and seed.

A comparison of pollen-mediated gene-flow estimates from established seedlings and from open-pollinated progeny arrays shows that realized pollen-mediated gene flow (12.5 to 17.5%) is a third or less than potential pollen-mediated gene flow (*4*). Therefore, accounting for seed dispersal and establishment is essential for determining actual genetic connectivity of extant populations. The situation for severely fragmented populations of *F. excelsior* is encouraging for the survival of a wind-pollinated, wind-dispersed species in fragmented habitats. Because of enhanced long-distance dispersal of both pollen and seed across a barren landscape, not only is genetic diversity maintained, but also new alleles are established into remnant gene pools (*6*). These characteristics may be important in allowing *F. excelsior* to adapt and shift range in response to climate change (*7*).

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Supporting Online Material

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New Neurons Follow the Flow of Cerebrospinal Fluid in the Adult Brain

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In the adult brain, neuroblasts born in the subventricular zone migrate from the walls of the lateral ventricles to the olfactory bulb. How do these cells orient over such a long distance and through complex territories? Here we show that neuroblast migration parallels cerebrospinal fluid (CSF) flow. Beating of ependymal cilia is required for normal CSF flow, concentration gradient formation of CSF guidance molecules, and directional migration of neuroblasts. Results suggest that polarized epithelial cells contribute important vectorial information for guidance of young, migrating neurons.

The structure and function of the central nervous system depends on precisely controlled movements of young neurons (*1*). Perhaps one of the most complex and far-reaching forms of neuronal migration occurs in the adult brain: Neuroblasts born in the subventricular zone (SVZ), next to the walls of the lateral ventricles, migrate to the olfactory bulb where they differentiate into local interneurons (*2*–*5*). In rodents, these young neurons first migrate in the SVZ, where they form a complex network of interconnected chains (*6*). Young neurons then join the rostral migratory stream (RMS), which leads them into the core of the olfactory bulb. It has been proposed that

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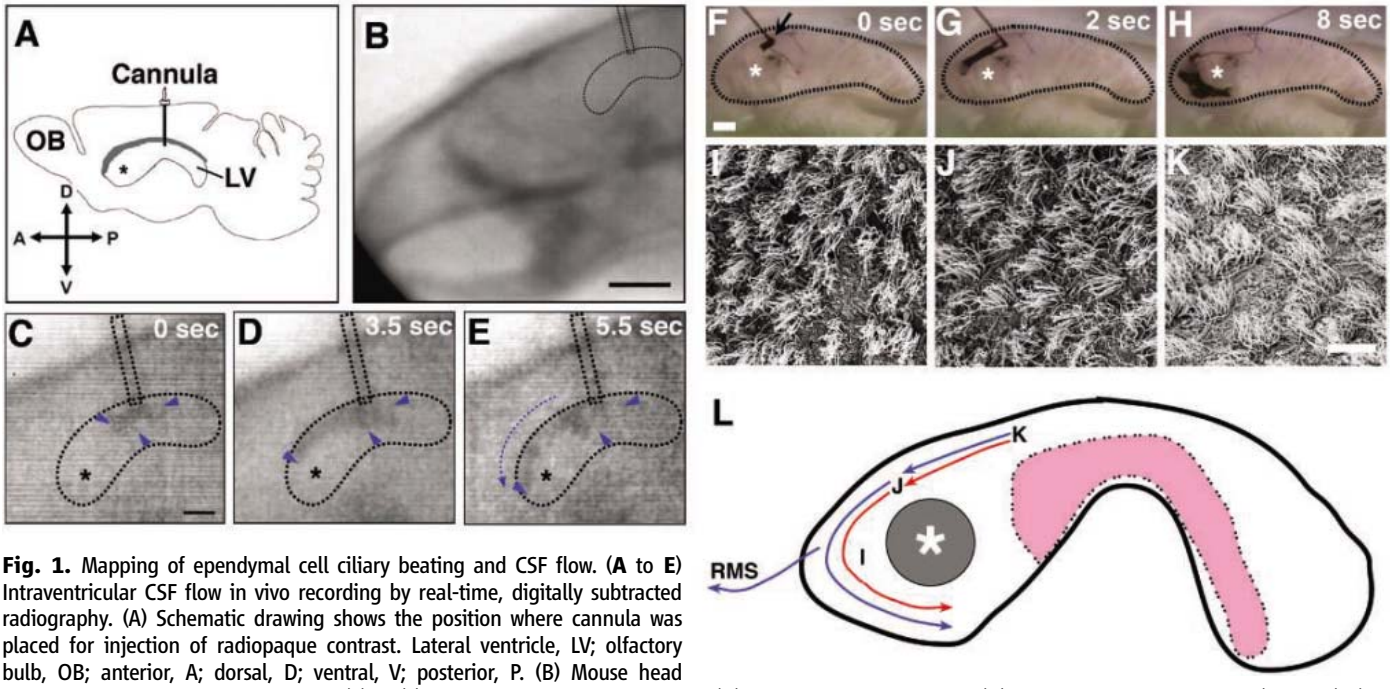

Fig. 1. Mapping of ependymal cell ciliary beating and CSF flow. (**A** to **E**) Intraventricular CSF flow in vivo recording by real-time, digitally subtracted radiography. (A) Schematic drawing shows the position where cannula was placed for injection of radiopaque contrast. Lateral ventricle, LV; olfactory bulb, OB; anterior, A; dorsal, D; ventral, V; posterior, P. (B) Mouse head radiogram before injection of contrast. (C) to (E) Serial radiograms were taken every 0.33 s. (C) At 0 s, (D) at 3.5 s, and (E) at 5.5 s. (See movie S1.) Dashed lines denote the lateral ventricle and cannula placement. Note how the contrast (arrowheads) moves along a dorsal corridor and then turns ventrally around the anterior horn (dashed arrow). The mean time of contrast movement to reach the anterior tip of the ventricle from the injection site (–1.0 mm relative to bregma) was 6.3 ± 0.8 s (SD) (n = 6). The site of the wall adhesion is marked by an asterisk. (**F** to **H**) Ependymal flow revealed by India ink placed [(F), arrow] onto exposed surface of the lateral wall of the lateral ventricle (n = 6). Note how ink moves along a dorsal corridor (G) and then turns ventrally (H) around the wall adhesion (asterisk). (See movie S2.) (**I** to **L**) Scanning electron micrographs showing orientation of ependymal cilia at various locations on the lateral wall of the lateral ventricle as indicated in (L). Cilia beat ventrally in the anterior part of the anterior horn (I), beat anteriorly in the dorsal anterior horn (J), and beat anterodorsally in the intermediate region dorsal to the choroid plexus (K). (L) Note how the direction of CSF flow (red) is similar to cell migration pattern (blue) (see Fig. 2) around the wall adhesion (asterisk). Scale bars: (B), 0.5 cm; (C) to (E), 0.15 cm; (F) to (H), 1 mm; (I) to (K), 10 μm. Pink denotes the location of choroid plexus.

Slit proteins expressed in septum (*7*, *8*) and choroid plexus (*9*) are the relevant chemorepulsive factors. Septum and choroid plexus are separated from the SVZ by the lateral ventricle filled with CSF and by the epithelial lining of the lateral ventricle, the ependyma. It is not understood how CSF guidance molecules reach the SVZ and form gradients in the adult brain. The ependyma is polarized with oriented bundles of motile cilia protruding into the lateral ventricle lumen (*10*, *11*). Coordinated, whiplike motion of epithelial cilia has been proposed to direct flow of mucosa and fluids in the trachea, oviduct, and ventricles (*12*).

Pattern of ependymal flow in the lateral ventricle. To record intraventricular CSF flow in vivo, we injected a contrast agent into the caudal lateral ventricle of adult mice (n = 6), which was detected by real-time fluoroscopy. The contrast agent injected into the ventricle moved rostrally along a dorsal corridor into the anterior horn and then ventrally around the adhesion area (Fig. 1, A to E; movie S1). Magnetic resonance imaging (MRI) (n = 10) of $MnCl_2$ secreted from the choroid plexus revealed similar CSF movement (fig. S2). To directly correlate the flow of CSF with the planar polarity of ependymal cells, we deposited a small amount of India ink onto the exposed surfaces of dissected walls of lateral ventricles (n = 6). The pattern of ink flow, generated by the beating ependymal cilia, paralleled that of CSF flow observed in vivo (Fig. 1, F to H; movie S2). Furthermore, the orientation of cilia beating observed live under the light microscope or, after fixation, by scanning electron microscopy was similar to the patterned flow observed in vivo and in vitro (Fig. 1, I to K) (*11*). These results indicate that ciliary beating and planar polarity of ependymal cells generate directed currents of fluid adjacent to the ventricular wall.

Neuroblast migration parallels CSF flow. There is a remarkable similarity between the direction of CSF flow and the organization of the network of chains of migrating neuroblasts in the SVZ (*6*) (Fig. 2A). To determine the orientation of migrating neuroblasts at different locations in the SVZ, we labeled neuroblasts by focal injections of a retrovirus encoding alkaline phosphatase. Direction of migration was inferred from the average orientation of the leading process (598 cells in 25 animals), a reliable indicator of SVZ neuroblast migration (*13*, *14*) (Fig. 2). As expected, of 184 cells in the RMS, 81.0% were oriented in the direction of the olfactory bulb. Likewise, in the dorsal SVZ, of 303 cells, 60.7% pointed in the direction of the RMS, an orientation equivalent to that of the CSF flow on the ventricular surface in this region. It was noteworthy that, in the anterior SVZ, only 20.7% of neuroblasts (of 111) pointed dorsally toward the RMS, whereas 45.9% were oriented in the ''reverse'' direction (P < 0.01, chi-square analysis) (Fig. 2, B and C), which parallels the flow of CSF (Fig. 1). Thus, the orientation of neuroblast migration correlates with the flow of CSF rather than with the relative position of the olfactory bulb.

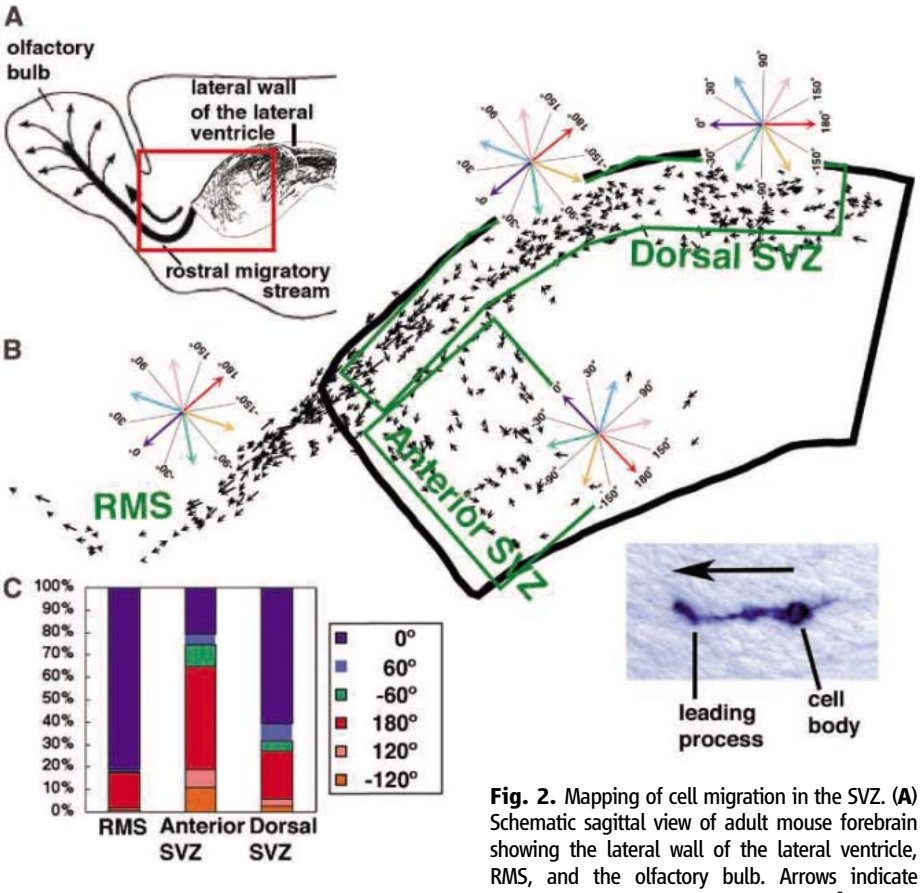

Fig. 2. Mapping of cell migration in the SVZ. (**A**) Schematic sagittal view of adult mouse forebrain showing the lateral wall of the lateral ventricle, RMS, and the olfactory bulb. Arrows indicate direction of migration. Camera lucida drawing of the chains of neuroblasts in the SVZ is included [modified from (*6*)]. (**B**) Composite map of the direction of cell migration (from 25 animals) in the SVZ (delineated by green rectangles) and RMS. Each black arrow in the map indicates the orientation and length of the leading process of individual cells. Neuroblasts were labeled with a retrovirus encoding alkaline phosphatase (see inset for example). (**C**) Quantification of cell migration. The orientation of the leading process of each cell was used to determine the percentage of cells oriented in the direction of the olfactory bulb (defined as 0°) [see compasses in (B)]. In the dorsal SVZ and in the RMS, 0° was defined in the direction of the olfactory bulb and parallel to the longitudinal array of chains. Cells pointing in the reverse direction were considered oriented at 180°. For the anterior SVZ, 0° orientation was defined dorso-anteriorly in the direction of the longitudinal array of chains leading to the olfactory bulb. Note in the histogram how the majority of cells in the dorsal SVZ and RMS have a 0° orientation (toward the olfactory bulb). In contrast, the majority of cells in the anterior SVZ are pointing ventrally (180°) away from the RMS and olfactory bulb. The total numbers of cells counted in each region: RMS, 184; anterior SVZ, 111; and dorsal SVZ, 303.

Ependymal flow is required for neuroblast orientation. To determine whether ependymal ciliary beating is required for normal SVZ cell migration, we studied *Tg737*^{orpk} mutant mice (*15*, *16*). These mice carry a hypomorphic allele for Polaris, which is essential for normal ciliogenesis. As a consequence, these animals have hydrocephalus, develop polycystic kidney disease, and show disruptions in left-right asymmetry (*15*, *16*). Ependymal cells cover the walls of the ventricles in *Tg737*^{orpk} mutant mice, but these cells had few, short, irregular cilia compared with ependymal cells in the wild type (fig. S3, A and B). Most of the mutant cilia were not motile (movie S3), and occasional motile cilia were not sufficient to produce CSF flow (movie S2). Fluoroscopic imaging in vivo also showed lack of normal CSF flow in *Tg737*^{orpk} animals (fig. S1, movie S1).

Neuroblasts stained with antibody against the polysialylated form of the neural cell adhesion molecule (PSA-NCAM) were found in the SVZ of *Tg737*^{orpk} mice, and these cells became organized into chains similar to those observed in wild-type mice (Fig. 3, A and B). Strikingly, however, chains in

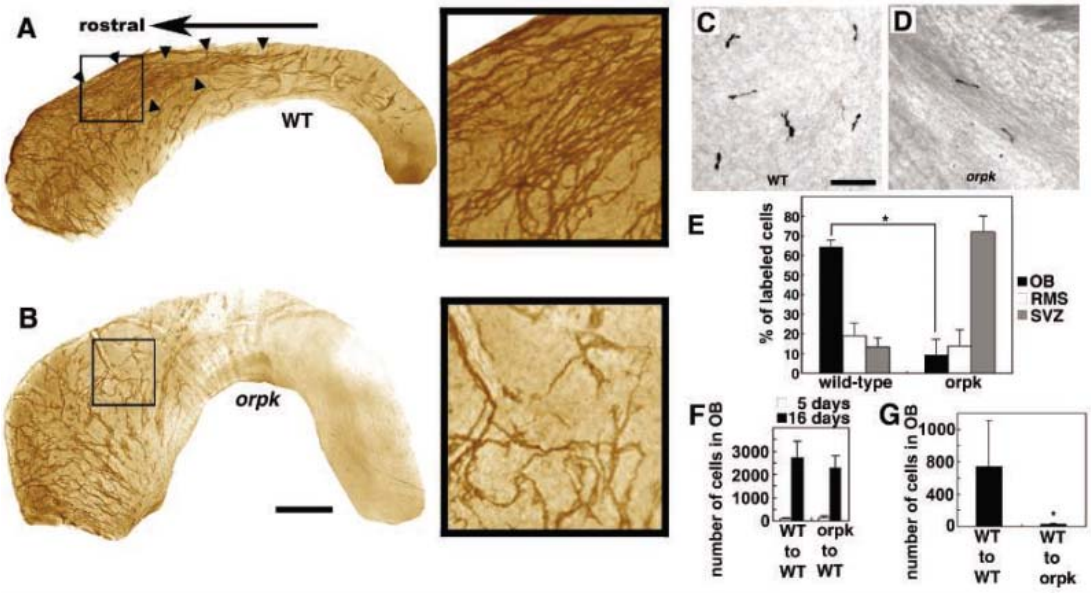

Fig. 3. Cell migration defects in the *Tg737*^{orpk} mutant. (**A** and **B**) Whole mounts of the lateral walls of the lateral ventricle stained with antibody against PSA-NCAM. A well-organized longitudinal array of chains (arrowheads) was observed in the wild-type brain (WT) (A) but not in the *Tg737*$^{orpk/orpk}$ mutant (B). Higher magnification views of the dorsal region marked by squares (A) and (B) are shown in the insets to the right. (**C** to **E**) Normal cilia are required for rostral migration of endogenous neuroblasts. Sagittal sections of wild-type (C) and *Tg737*^{orpk} (D) olfactory bulbs 5 days after injection of alkaline phosphatase–encoding retrovirus into the SVZ. (E) The number of alkaline phosphatase^{+} cells (means ± SD) reaching the olfactory bulb in the *Tg737*$^{orpk/orpk}$ mice was significantly smaller than in the wild type ($P = 0.0004$, *t* test). Total number of cells counted: wild type, 396 ($n = 3$); mutant, 112 ($n = 3$). (**F**) *Tg737*$^{orpk/orpk}$ mutant neuroblasts can migrate normally in the wild-type brain. SVZ cells from wild-type or *Tg737*$^{orpk/orpk}$ mutant mice carrying GFP were grafted into the SVZ of wild-type brains. (See fig. S4.) The histogram shows the number of GFP^{+} cells (means ± SD) in the olfactory bulbs 5 days ($n = 4$) and 16 days ($n = 4$) after transplantation. No significant difference was observed ($P = 0.7763$ at day 5 and 0.422 at day 16, *t* test). (**G**) Wild-type neuroblasts failed to migrate normally in the *Tg737*$^{orpk/orpk}$ mutant brain. GFP-labeled SVZ cells from wild-type mice were grafted into the SVZ of wild-type and *Tg737*$^{orpk/orpk}$ mutant mice. (See fig S4.) The histogram shows the number of GFP^{+} cells in the olfactory bulbs 5 days after transplantation (means ± SD) ($n = 4$). The number of wild-type cells reaching the olfactory bulb in the *Tg737*$^{orpk/orpk}$ brain was significantly smaller than in the wild type to wild type transplantation controls ($P = 0.048$, *t* test). OB, olfactory bulb. Scale bars: (A) and (B), 1 mm; (C) and (D), 50 μm.

Tg737^{orpk} mice were severely disoriented compared with those of wild-type mice. This derailing was most noticeable in the dorsal SVZ, where in wild-type animals the majority of chains were oriented longitudinally. In *Tg737*^{orpk} mice, chains in this region were oriented in multiple directions, including many chains oriented perpendicular to their normal longitudinal orientation (Fig. 3, A and B). Chain disorientation was observed in all *Tg737*^{orpk} mice analyzed ($n = 3$). Proliferating and pyknotic cells in the SVZ and RMS of *Tg737*^{orpk} mice were found in locations and in numbers similar to those of wild-type animals (fig. S3). However, *Tg737*^{orpk} mice develop hydrocephalus because of the lack of normal CSF flow, and this ventricular expansion could have induced chain disorientation. As a control, we induced obstructive hydrocephalus in wild-type mice by partial surgical obstruction of the aqueduct of Sylvius, a manipulation that did not affect the pattern of ink flow on the lateral ventricular wall. In these animals, the orientation of chains was not affected (*17*), which suggests that hydrocephalus alone was not the cause of disoriented chains.

To study the migration of neuroblasts from the SVZ into the olfactory bulb in *Tg737*^{orpk} mice, we labeled cells in the SVZ with an alkaline phosphatase–encoding retrovirus (Fig. 3, C to E). By 5 days after injection, 64.6% of the alkaline phosphatase–positive cells had reached the olfactory bulb in the wild-type littermates ($n = 3$). In contrast, in the *Tg737*^{orpk} mutant ($n = 3$), only 9.3% of the cells were found in the olfactory bulb, and 73.4% remained in the SVZ. Of the few neuroblasts ($n = 18$) that reached the RMS and olfactory bulb in the *Tg737*^{orpk} mutant, 77.8% were oriented in the forward direction, which suggests that normal ependymal cilia are required for proper migration of neuroblasts along the SVZ network, but not in the RMS or olfactory bulb. *Tg737*^{orpk} mutant neuroblasts carrying green fluorescent protein (GFP) were able to migrate normally to the olfactory bulb when grafted into wild-type SVZ ($n = 4$) (Fig. 3F; fig. S4, A to D). In contrast, few GFP^{+} wild-type cells grafted into the *Tg737*^{orpk} mutant SVZ ($n = 4$) reached the olfactory bulb (Fig. 3G; fig. S4, E and F). These grafting experiments indicated that *Tg737*^{orpk} mutation disturbs directional neuroblast migration in a manner that is not cell autonomous. Although we cannot totally exclude an indirect effect from chronic hydrocephalus or other defects in *Tg737*^{orpk} mutant animals on SVZ neuroblast migration, the above experiments strongly suggest that the absence of appropriate ependymal flow in *Tg737*^{orpk} mutant animals results in disorientation of SVZ neuroblast migration.

Ependymal flow is required for formation of chemorepulsive gradients in the SVZ. How might guidance cues be presented to migrating SVZ neuroblasts in vivo? CSF is secreted mainly from the choroid plexus, located in the caudal regions of the lateral ventricle (Fig. 1L). The choroid plexus is a source of chemorepulsive factors, including members of the Slit family, which influence SVZ cell migration (*9*, *18*). Ependymal cells allow access of CSF proteins or exogenous tracers to the underlying brain parenchyma (*19*, *20*). To determine how Slit proteins in CSF become distributed in vivo, we infused a recombinant Slit2–alkaline phosphatase fusion protein (Slit2-AP) into the caudal lateral ventricle close to the choroid plexus ($n = 5$) (Fig. 4, A to F). Slit2-AP protein was found not only on the surface of the ependymal layer, but also within the SVZ (Fig. 4, C and D). Importantly, the alkaline phosphatase signal was found in a gradient along the dorsal SVZ, with the highest signal in the caudal region (Fig. 4D), and progressively weaker signal was detected rostrally (Fig. 4, B and C). Remarkably, the gradient corresponds to the ventricular region of greatest forward CSF flow and to the SVZ area in which neuroblasts form longitudinal arrays of chains and migrate predominantly in a rostral direction (Fig. 4A). In contrast, the normal concentration

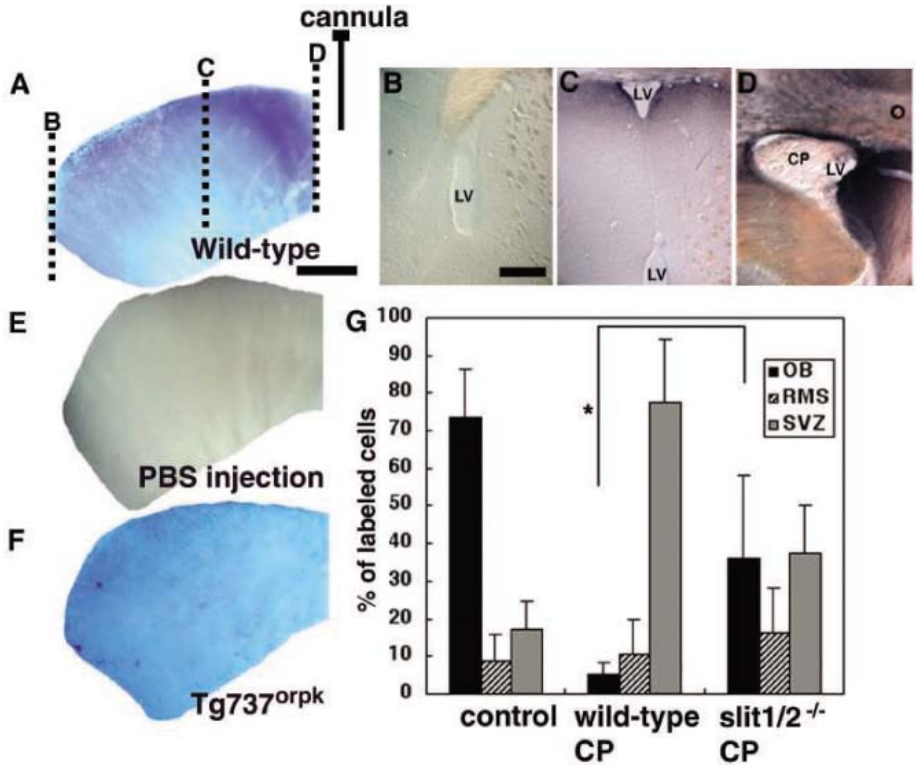

Fig. 4. Slit2-AP concentration gradient formation in the SVZ. (**A** to **F**) The Slit2-AP fusion protein was infused into the caudal lateral ventricle close to the choroid plexus in wild-type [(A) to (D)] (n = 5) and *Tg737*^{orpk} mutant (F) (n = 3) brains. Whole mounts of the lateral ventricular wall (anterior horn) [(A), (E), and (F)] or coronal sections [(B) to (D)] were stained for alkaline phosphatase enzyme activity 24 hours after the beginning of infusion. (E) Phosphate-buffered saline injection resulted in no signal (n = 1). (B) to (D) correspond to three different rostrocaudal levels of an infused brain sectioned in the coronal plane as shown approximately by the dotted lines in (A). Slit2-AP was deposited in a gradient, with the highest alkaline phosphatase activity detected in the caudal and dorsal SVZ. (F) Injection of Slit2-AP into the caudal lateral ventricle of Tg737^{orpk} mutants did not result in the formation of this gradient. (**G**) *Slit1/2* mutant (n = 5) or wild-type (n = 4) choroid plexuses were transplanted dorsal to the RMS. (See fig. S5.) As a control, meninges (n = 4) were grafted in the same location. One month later, alkaline phosphatase–encoding retrovirus was injected into the SVZ. Five days after injection, alkaline phosphatase$^+$ cells (means ± SD) were counted. In controls, most of the alkaline phosphatase–labeled cells have reached the olfactory bulb, with few cells remaining in the SVZ and RMS. The pattern was reversed in the choroid plexus–grafted (CP) animals; most of the cells failed to reach the olfactory bulb and remained in the SVZ. This repulsive effect of the choroid plexus graft was partially reversed in the Slit1/2 mutant (P = 0.0068, t test). OB, olfactory bulb. Scale bars: (A), (E), and (F), 1 mm; (B) to (D), 0.5 mm.

gradient did not form when Slit2-AP was injected into the lateral ventricle of *Tg737*^{orpk} mutants (n = 3) (Fig. 4F). These results indicate that CSF flow is necessary for the formation of the Slit2 gradient in the SVZ in vivo.

Anterior grafts of choroid plexus disrupt rostral neuroblast migration. To test whether disruption of a concentration gradient of chemorepulsive factors secreted by choroid plexus affects directional neuroblast migration in vivo, we transplanted a fragment of wild-type or *Slit1/2* mutant choroid plexus anteriorly, just dorsally to the RMS (fig. S5Q). RMS morphology, retroviral injection, and cell transplantation indicated that wild-type choroid plexus anterior to the SVZ inhibits most, if not all, of the rostral migration of the neuroblasts into the olfactory bulb (fig. S5). The number of retrovirally labeled alkaline phosphatase$^+$ cells reaching the olfactory bulb was significantly greater in animals with a grafted *Slit1/2* mutant choroid plexus (n = 6) than in animals that received a similar-size, wild-type choroid plexus graft (n = 8) (Fig. 4G). This indicates that Slit proteins contribute to the choroid plexus's repulsive activity in vivo. Interestingly, animals with *Slit1/2* mutant choroid plexus grafts had fewer alkaline phosphatase$^+$ cells in the olfactory bulb than mice that received no grafts or control grafts of meninges (Fig. 4G), which suggests that additional factors expressed in choroid plexus, such as Slit3 (*21*), may be responsible for the residual choroid plexus repulsive activity.

Our results suggest that the planar polarity of ciliated ependymal cells is essential for the formation of chemorepulsive–factor gradients that guide neuroblast migration in the adult brain. Previous work, which implicated nodal cilia in the determination of left-right asymmetry (*22*), indicates that polarized ciliated cells contribute important vectorial information for body plan development. The present work suggests that polarized epithelia and motile cilia in the brain serve as important conveyors of directional information for neuronal migration.

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Materials and Methods
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Movies S1 to S3

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The Large-Scale Axisymmetric Magnetic Topology of a Very-Low-Mass Fully Convective Star

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Understanding how cool stars produce magnetic fields within their interiors is crucial for predicting the impact of such fields, such as the activity cycle of the Sun. In this respect, studying fully convective stars enables us to investigate the role of convective zones in magnetic field generation. We produced a magnetic map of a rapidly rotating, very-low-mass, fully convective dwarf through tomographic imaging from time series of spectropolarimetric data. Our results, which demonstrate that fully convective stars are able to trigger axisymmetric large-scale poloidal fields without differential rotation, challenge existing theoretical models of field generation in cool stars.

Magnetic fields of cool stars are supposedly produced and sustained through dynamo processes operating in their outer convective envelopes and involving both differential rotation and turbulence (*1*). Differential rotation winds up an initially poloidal field, generating a toroidal field, and then cyclonic turbulence acting on the toroidal field regenerates a poloidal field of opposite polarity, which ends the first half of the so-called "magnetic activity cycle." In partly convective Sun-like stars, dynamo processes presumably concentrate where differential rotation is strongest (*2*), at the interface layer between their radiative cores and convective envelopes (*3*, *4*). In fully convective stars, however, the lack of such layers has led theoreticians to propose that their strong magnetism may be due to dynamo processes of other kinds (*5*–*7*). Recent models disagree on the type of large-scale magnetic topologies that fully convective stars can generate; whereas some conclude that very-low-mass stars should produce nonaxisymmetric noncyclic fields and negligible differential rotation (*8*–*10*), others predict they should trigger substantial differential rotation and mainly axisymmetric, oscillatory fields (*11*, *12*). This disagreement essentially reflects the fact that existing numerical models of stellar dynamos must rely on various simplifications that can distort their results. Realistic models remain beyond the reach of high-performance computing.

Observing magnetic topologies of very-low-mass dwarfs is thus critical to progress in this field. Existing data demonstrate that fully convective stars, especially the rapidly rotating ones, are strongly magnetic and show both indirect and direct evidence for the presence of fields in their atmospheres (*13*–*16*). The broadening that fields induce in unpolarized spectral lines through the Zeeman effect (*17*) indicates that magnetic fields of several kilogausses are present at the surface of very-low-mass dwarfs (*15*, *16*). However, distinguishing among the various existing theoretical models requires maps of the vector magnetic field over the stellar surface. Because line-broadening measurements are poorly informative on the field topology, the best solution is to analyze the polarization signatures that magnetic fields generate in spectral lines through the Zeeman effect (*17*). Sensing both the magnetic flux and the field orientation, this complementary method has proved very successful for detecting the fields of active stars and estimating their topologies (*18*, *19*). Thus, it optimally suits the present needs.

During three nights of observation (18, 20, and 22 August 2005) with the high-efficiency high-resolution spectropolarimeter Echelle SpectroPolarimetric Device for the Observation of Stars (ESPaDOnS) (*17*, *20*) recently installed on the Canada-France-Hawaii Telescope, we obtained 64 circularly polarized spectra sampling three nonconsecutive rotation cycles of V374 Peg, a rapidly rotating M4 dwarf with a low enough mass (≈0.28 $M_\odot$ where $M_\odot$ is the mass of the Sun) (*21*) to ensure convection throughout the whole star

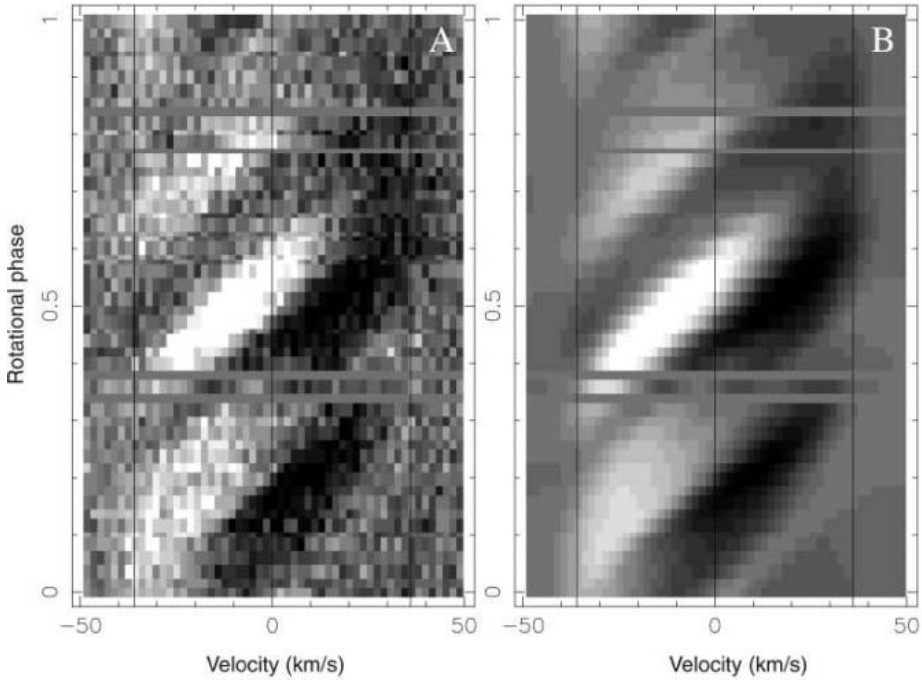

Fig. 1. Dynamic Stokes *V* spectrum of V374 Peg phased to a rotation period of 0.4456 days. (**A**) LSD profiles derived from observations. (**B**) Fit to the data obtained with our magnetic imaging code. The vertical lines depict the blue edge, center, and red edge of the rotationally broadened line profile of V374 Peg (in the star velocity rest frame). Zeeman signatures migrate throughout the profile from negative to positive velocities (thus producing slanted tracks in the dynamic spectrum) as parent magnetic regions are carried across the visible hemisphere (from the approaching limb to the receding limb) by rotation. Black and white correspond to relative circular polarization levels of −0.3 and +0.3%, respectively.

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(*22*). Using least squares deconvolution (LSD) (*17*, *18*), we extracted the polarization information from about 5000 spectral lines simultaneously and produced mean Stokes *I* (unpolarized) and *V* (circularly polarized) profiles of V374 Peg for all collected spectra. Whereas unpolarized LSD profiles provide information about cool spots on the stellar surface through the shape distortions they produce (*23*, *24*), Stokes *V* profiles sound the surface magnetic topology through the Zeeman signals it induces in spectral lines (*25*–*27*). Strong magnetic signatures with amplitudes of up to 0.5% of the unpolarized continuum were detected from V374 Peg; unpolarized profile distortions from cool spots were very weak.

Matching unpolarized profiles required that the equatorial rotation velocity v_{eq} of V374 Peg is equal to $v_{eq}\sin i = 36.5 \pm 0.3$ km/s (where i is the angle between the rotation axis and the line of sight, and the error is ±SD) and that its heliocentric radial velocity is –3.9 ± 0.1 km/s. We found that the Zeeman signatures and their temporal variations repeat every ≈10.7 hours, a time scale consistent with the rotation period. What we observed is thus truly rotational modulation, with a period of $P_{rot} = 0.4456 \pm 0.0002$ days. The dynamic circular polarization spectrum, phased to the stellar rotation cycle (Fig. 1), shows clear Zeeman signatures migrating throughout the line profile from negative to positive velocities as the corresponding magnetic regions are carried across the visible hemisphere (from the approaching limb to the receding limb) by rotation. Three such signatures can be straightforwardly identified from Fig. 1: a main signature crossing line center at phase 0.5 and two weaker signatures at phase 0.20 and 0.75. The line-of-sight projected (longitudinal) component of the magnetic field, computed from the first-order moment of the Zeeman signature (*18*), is always positive and peaks at 350 G (at phase 0.5). From P_{rot} and $v_{eq}\sin i$, we derived that the radius R of V374 Peg verifies $R\sin i = 0.32\ R_\odot$ (where $R_\odot$ is the radius of the Sun); from the absolute magnitude in the K photometric band (≈7.0), we found that $R \leq 0.37\ R_\odot$ (*28*) and thus concluded that $i \geq 60°$ (i.e., the rotation axis is almost perpendicular to the line of sight). Given the unlikelihood that i exactly equals 90°, we assume here that $i = 70°$ (results are similar for $60° \leq i \leq 80°$).

Using tomographic imaging techniques (*17*), we can reconstruct detailed surface maps of rapidly rotating stars, such as V374 Peg, from time-resolved series of rotationally modulated profiles of spectral lines (*23*–*27*). We used a stellar-surface imaging code based on spherical harmonics decomposition and maximum entropy principles (*29*) to reconstruct a model of the stellar magnetic topology that reproduced the observed Stokes *V* dynamic spectrum. The typical longitudinal resolution achieved at the equator is ≈10° or ≈0.03 rotation cycles. Under the assumption that the field is potential, we obtained a synthetic Stokes *V* dynamic spectrum (Fig. 1) matching the data at noise level. No notable improvement was obtained when assuming that the field also includes a toroidal component. The recovered topology (Fig. 2) features mostly radial field, with areas where magnetic strengths reach 2 kG. Azimuthal and meridional field features are typically four times weaker. As expected from the Zeeman signatures, which feature constant signs throughout the rotation cycle, the latitudinal polarity pattern of the reconstructed radial field map is simple, with positive fields occupying most of the upper stellar hemisphere (where the method sensitivity to radial fields is highest).

With observations of three rotation cycles sequentially shifted by 4.5 cycles, we can estimate the amount of differential rotation shearing the surface of V374 Peg. We assumed that the rotation rate at the surface of V374 Peg depends mostly on latitude θ and varies as $\Omega_{eq} - d\Omega\sin^2\theta$, where Ω_{eq} is the angular rotation rate at the equator and $d\Omega$ is the difference in angular rotation rate between the equator and pole. We found that optimal fits to the data (*17*) are achieved for $d\Omega = 0 \pm 0.02$ rad/day (68% confidence interval), and thus that the rotation of V374 Peg is compatible with solid body rotation (Fig. 3). It implies that V374 Peg needs at least 1 year for its equator to lap the pole by one complete turn (i.e., more than three times as much time as the Sun). This is compatible with recent results indicating that surface differential rotation is apparently vanishing almost completely in very-low-mass stars (*30*).

Although no measurement has been published yet for V374 Peg itself, magnetic field estimates derived from Zeeman broadening of unpolarized profiles (*17*) exist for a few similar mid-M dwarfs (*16*), indicating that

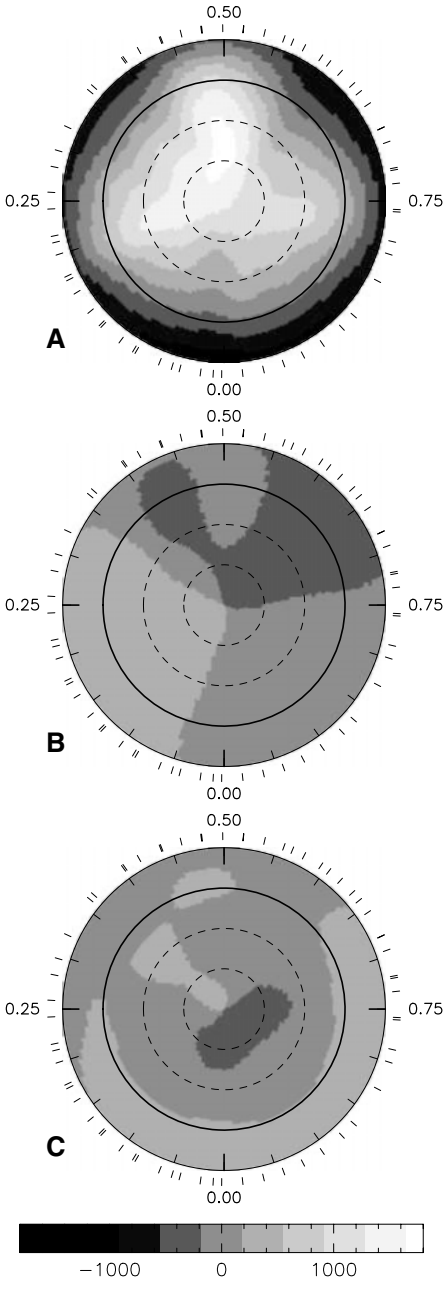

Fig. 2. The mostly radial magnetic topology at the surface of V374 Peg, reconstructed from our observations. (**A**) Radial field component. (**B**) Azimuthal field component. (**C**) Meridional field component. The star is shown in flattened polar projection down to latitudes of –30°, with the equator depicted as a bold circle and parallels as dashed circles. Phase coordinates are noted around each plot, with external radial ticks indicating observations. Black and white correspond to field strengths of –1.8 and 1.8 kG, respectively.

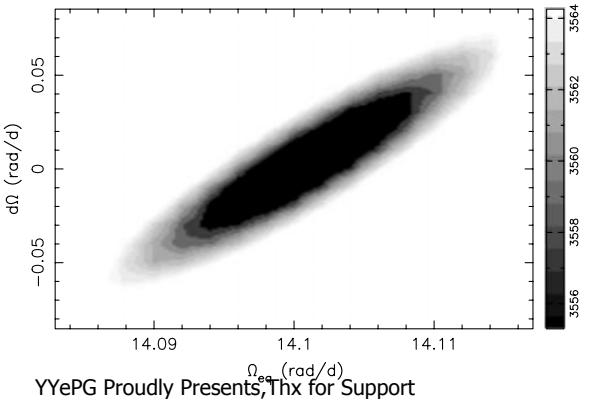

Fig. 3. Variation of statistical χ^2 with differential rotation parameters Ω_{eq} and $d\Omega$. The total number of fitted data points is ≈3500, implying that the gray ellipse (enclosing points with $\Delta\chi^2 \leq 9$) projects on each axis into confidence intervals of 99.7%. Rotation of V374 Peg is compatible with solid-body rotation at a rate of 14.100 ± 0.004 rad/day. Black and white correspond to χ^2 values of 3555.3 ($\Delta\chi^2 = 0$) and 3564.3 ($\Delta\chi^2 = 9$), respectively.

about half the stellar surface is covered with field strengths of 3 to 4 kG (overall magnetic fluxes of 1.5 to 2 kG). The average field flux we report here is about 0.5 to 1 kG, indicating that the method we used likely underestimates the actual field strengths of V374 Peg. The likely explanation is that the method we used, although successful at recovering the field topology on spatial scales larger than the resolution element (about 10° in longitude at the equator), fails at detecting very-small-scale multipolar magnetic groups whose average Zeeman signature [sensitive to the vector properties of the field (*17*)] is zero. We thus conclude that the magnetic field of V374 Peg probably includes both a large-scale structure that we are able to detect and map, and a very-small-scale, highly multipolar structure that remains inaccessible to us. Because our aim was to compare the large-scale field structure with that predicted by numerical dynamo models, this limitation was not a problem for our study.

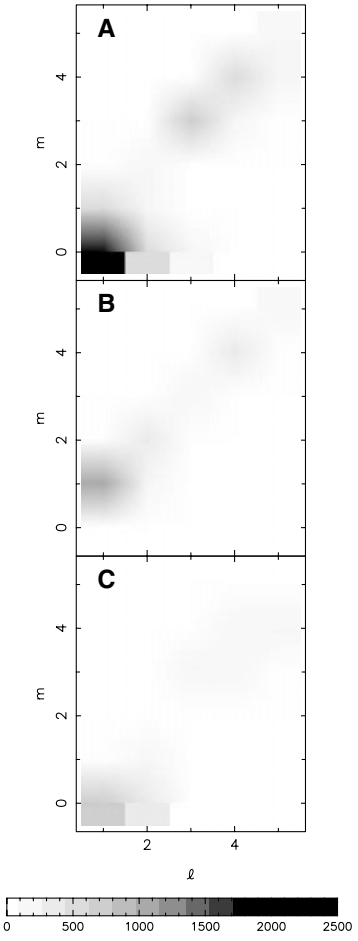

Fig. 4. Mode amplitude in the spherical harmonics expansion of the reconstructed magnetic field distribution, as a function of mode degree ℓ and order m. (**A**) Radial field component. (**B**) Azimuthal field component. (**C**) Meridional field component. The strongest mode corresponds to a dipole aligned with the rotation axis, with an amplitude of ≈3 kG. Only modes with orders and degrees lower than 5 are shown here. White and black correspond to mode amplitudes of 0 and 2.5 kG, respectively.

Our image shows several notable differences with magnetic maps of active stars that are not fully convective (*19*). Whereas magnetic topologies of partly convective stars almost always involve a strong and dominant toroidal field component at the stellar surface, without which the Stokes V data cannot be reproduced (*19*, *29*), the field of V374 Peg includes no such feature and can be modeled as a purely potential structure. Strong large-scale toroidal fields are systematically observed in the photosphere of active stars featuring (even small) differential rotation (*31*), which further strengthens our findings that V374 Peg rotates mostly as a solid body and confirms the claim that differential rotation vanishes in fully convective stars (*30*). Another important difference is that the potential field of V374 Peg is about an order of magnitude stronger than that of partly convective stars (*19*), with a typical strength of several kilogausses as opposed to a few hundred gausses for other active stars. Its large-scale spatial structure is also much simpler, with monopolar regions covering up to one hemisphere (far larger than the resolution element).

The spherical harmonics expansion of the recovered magnetic field distribution (Fig. 4) reveals that the dominant mode excited in V374 Peg by dynamo processes corresponds to a dipole aligned with the rotation axis (spherical harmonics degree $\ell = 1$ and order $m = 0$) whose amplitude reaches ≈3 kG. Power from this mode is leaking into the $\ell = m = 1$ mode, reflecting the offset of the main radial field region with respect to the pole. Several other modes, and in particular sectorial modes ($\ell = m$), are also detected on V374 Peg; the $\ell = m = 1$ and $\ell = m = 3$ modes are clearly visible on the reconstructed azimuthal and radial field maps, respectively (Fig. 2). All are, however, at least 2.5 times weaker than the main axisymmetric mode seen on V374 Peg. Little power is detected for modes with degrees larger than 5 despite our ability to recover modes with up to $\ell = 18$, emphasizing again that the magnetic features detected on V374 Peg are far larger than the resolution element.

This result challenges the most recent theoretical models of fully convective stars (*8*–*12*). On one side, models predicting no surface differential rotation, in agreement with observations, conclude that dynamo processes should only produce nonaxisymmetric large-scale fields (*8*–*10*), in contradiction with our result. On the other side, dynamo models that succeed at producing large-scale axisymmetric fields, in rough qualitative agreement with our findings, predict marked surface differential rotation (*11*, *12*), in contradiction with our observations. Moreover, such models predict that the toroidal component of the dynamo field should dominate, even at photospheric level, which again is not supported by our observations. We thus conclude that existing numerical dynamo models, even though rather elaborated, are not yet close enough to reality to predict successfully the magnetic topologies of convective stars; spectropolarimetric observations of a large sample of cool stars with ESPaDOnS should provide the strong observational constraints that models require.

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Optical Signatures of Coupled Quantum Dots

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An asymmetric pair of coupled InAs quantum dots is tuned into resonance by applying an electric field so that a single hole forms a coherent molecular wave function. The optical spectrum shows a rich pattern of level anticrossings and crossings that can be understood as a superposition of charge and spin configurations of the two dots. Coulomb interactions shift the molecular resonance of the optically excited state (charged exciton) with respect to the ground state (single charge), enabling light-induced coupling of the quantum dots. This result demonstrates the possibility of optically coupling quantum dots for application in quantum information processing.

Semiconductor approaches to quantum information can leverage the industry's vast technological infrastructure and integrate with existing information and communication technologies. Quantum dots (QDs) are an attractive host for storing a quantum information bit (qubit), because their atom-like properties (*1*) can be engineered through modern nanofabrication and crystal growth techniques (*2*–*5*). Advances in the fabrication and physics of single quantum dots (SQDs), together with the need for scalable qubit arrays (*6*, *7*), have recently brought coupled quantum dots (CQDs) to the foreground. Electron transport measurements on CQDs have demonstrated spin-sensitive coupling and manipulation of electron and nuclear spins (*8*–*10*), and optical spectra of coupled excitons have been measured (*11*–*14*) and calculated (*15*–*19*) in self-assembled CQDs.

Optical spectroscopy is a powerful tool for probing and manipulating QDs. Many of the methods of atomic physics can be used, including coherent manipulation (*20*, *21*) and optical orientation (*22*–*24*). Although coupled excitons in a single QD have been used to demonstrate a two-qubit gate (*21*), an optical architecture ultimately requires long-lived qubits such as the spin of an unpaired electron (*23*, *24*) or hole (*25*). This would then have the advantage that optically excited states could be used as auxiliary levels for ultrafast control of the qubits.

We present the optical spectrum of a CQD containing a single extra charge. In analogy with the transport systems (*8*–*10*) and with recent CQD exciton studies (*13*, *14*), we use an applied electric field to convert between molecular and atomlike orbital states. Our experiments reveal a distinct molecular state for the extra charge alone and another for its optically excited state (trion, or singly charged exciton). Spin leads to well-resolved singlet and triplet transitions in the anticrossing region of the charged exciton.

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Our InAs QDs are grown by molecular beam epitaxy using an indium flush technique (*2*, *3*, *26*). After a thin GaAs tunneling barrier of thickness d, a second layer of QDs nucleates preferentially above the first layer of dots, forming CQDs (*4*, *5*). In some cases, the two dot layers are grown with substantially different heights to separate the optical transitions and to distinguish between the individual dots in an asymmetric CQD pair. The QDs are embedded in a n^+-intrinsic-Schottky diode (Fig. 1A) to apply an electric field and to control the charging (*27*). To study individual CQDs, photoluminescence (PL) was excited and detected at ~10 K through aluminum shadow masks with 1-μm-diameter apertures.

The PL energy dispersion as a function of applied field for SQDs and CQDs show marked differences (Fig. 2). Nevertheless, there are similarities in their electric field dependence, charging, and binding energies. The SQD pattern has been well understood as a series of excitons that shift discretely in energy as the charge state changes (*27*, *28*). We identify the neutral exciton (X^0) (a single electron and hole), a positively charged exciton (X^{+1}) that contains an additional hole and lies within a few meV of X^0, and a series of negatively charged excitons starting with the negative trion (X^{-1}) ~ 6 meV to lower energy. This qualitative pattern of discrete energy shifts is also observed in the CQDs, as expected for direct recombination in the lower energy dot of an asymmetric CQD pair (Fig. 1B). Additionally, we observe transitions with large electric field dependences (Stark shifts) and intriguing patterns of crossings and anticrossings in Fig. 2, A and B.

The exciton energies and transitions for the lower energy dot ("B") of an asymmetric CQD pair are shown schematically as a function of electric field in Fig. 1C. Away from the crossing point, the direct recombination ($^{10}_{10}X^0$), which arises from the electron and hole recombining primarily in the same dot, has a weak Stark shift. In contrast, the indirect recombination ($^{10}_{01}X^0$) arising from the electron and hole localized on different dots (*13*, *14*) displays a strong linear Stark shift, $\Delta E = e[d + (h_B + h_T)/2)]F$, where the slope depends on barrier thickness (d) and where F is the electric field. When the direct and indirect transition energies of an asymmetric CQD approach each other, either the electron or hole levels in the two dots become resonant, the wave functions become delocalized over both dots, and the transitions show anticrossing behavior. Away from these anticrossings the wave functions retain their single dot character. The anticrossing splitting depends on the tunneling rates, which in turn depend on barrier thickness and carrier mass. For the neutral exciton, we observe an indirect transition with a strong Stark shift and an anticrossing (Δ_{X^0} in Fig. 2B), consistent with recent reports (*13*, *14*).

The asymmetric nature of these CQDs simplifies our interpretation of their spectra, because electron and hole resonances occur at different fields and can therefore be considered independently. For these CQDs, the bottom dot ("B") has a smaller direct transition energy than the top dot ("T"), as represented in Fig. 1B.

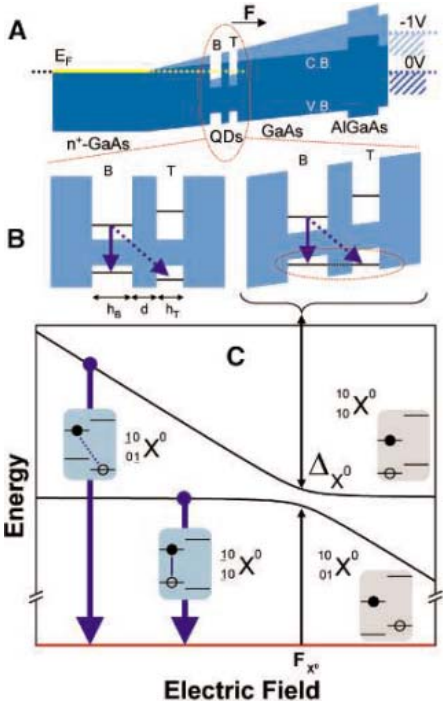

Fig. 1. (**A**) Band-edge diagram of the device layer structure. The two dots are labeled bottom (B) and top (T). Electric field direction, F, is also indicated. (**B**) Schematic of the CQD region at flat-band condition and at the field (F_{X^0}) where a hole resonance occurs. The direct (solid arrow) and indirect (dashed arrow) transitions are indicated. (**C**) Diagram of the X^0 initial state (black lines) and final state (red line, vacuum state) for dot B. The direct ($^{10}_{10}X^0$) and indirect ($^{10}_{01}X^0$) recombinations are indicated. The states are labeled $^{e_B e_T}_{h_B h_T}X^Q$, where the left superscripts (subscripts) give the number of electrons (holes) in the bottom e_B (h_B) and top e_T (h_T) dots and Q is the total charge of the system. The transitions are indicated by underlining the recombining carriers.

With this ordering, a larger electric field (higher reverse bias) brings the hole levels into resonance, whereas the electron levels become detuned and the electron remains localized (Fig. 1B, right). By inverting the order of the dots, i.e., smaller energy on top, we have been able to reverse this behavior and to observe the case of electron level resonance. For a CQD with a barrier thickness of 4 nm, we calculate and measure electron anticrossing splittings that are an order of magnitude larger than for holes (e.g., 4.5 versus 0.42 meV). We discuss only results from samples with hole level resonances, such that the anticrossing energies are small (<1 meV), and the charging pattern in the molecule can be easily compared with that of SQDs.

Introducing a single additional charge into the CQD dramatically enriches the spectrum (Fig. 2, box A), where we observe an intricate X-shape pattern with several anticrossing splittings close to 1 meV. The dominant features arise from a strong indirect transition ($^{10}_{11}X^{+1}$ with high Stark shift) that anticrosses two direct transitions ($^{10}_{20}X^{+1}$, $^{10}_{11}X^{+1}$ with small Stark shifts). There is also a weaker indirect transition of opposite slope that appears only between the anticrossings. Comparison with the electric field dependence of the SQD PL in Fig. 2 suggests that the spectral structure a few meV above $^{10}_{10}X^{0}$ results from a positively charged exciton state (positive trion). Anticrossings may occur only between states with the same total charge, so it follows that all of the features in this structure also arise from a positively charged exciton state (Fig. 2, box A). In contrast, the neutral exciton ($^{10}_{10}X^{0}$) passes unaffected through the anticrossing region of the positively charged exciton state. Similarly, $^{10}_{11}X^{+1}$ passes unaffected through the neutral exciton anticrossing region (Fig. 2, box B). To explain the details of the pattern in Fig. 2, box A, we now analyze the possible configurations for the three charges of a positively charged exciton in a coupled dot system.

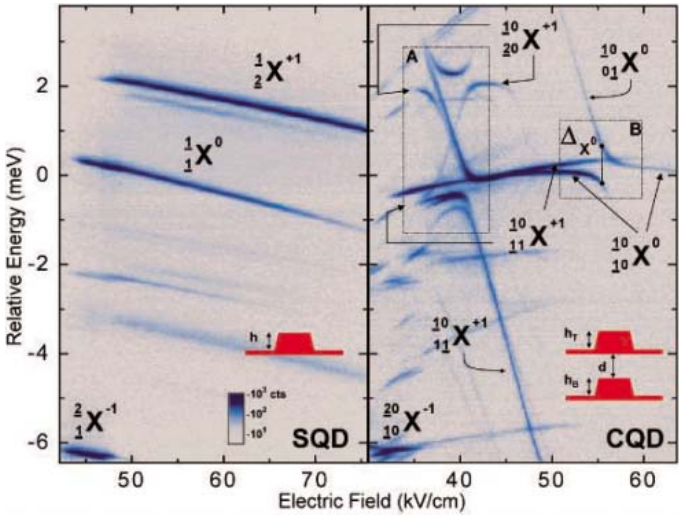

Fig. 2. Comparison of electric field–dependent photoluminescence spectra for a single QD (SQD) (left) and coupled QD (CQD) (right). We note the similarities such as field dependence, binding energies, and negative charging behavior, along with the observation of extraordinary Stark shift lines ($^{10}_{11}X^{+1}$, $^{10}_{01}X^{0}$), which show both crossing and anticrossing behavior. Box B shows the region of neutral exciton (X^0) anticrossing. Detail resulting from a positively charged exciton (X^+) in the CQD is displayed in box A. The insets are schematic cross sections of the two sample structures. CQD structures in this study are identified by the sequence of numbers $h_B/d/h_T$ corresponding to the height of the bottom dot, barrier thickness, and height of the top dot, all in nm. In this figure, the samples are ($h_B/d/h_T$) = (2.5/4/2.5) and for the SQD h = 3.5 nm. As in all figures, spectra are plotted as log(Intensity).

We can understand the basic structure of the spectrum with a simplified energy-level diagram that does not include tunneling and spin (Fig. 3A). For a single hole there are two configurations (red lines), with the hole in one or the other of the dots. The charged exciton has six possible configurations (i.e., three particles in two dots), but the electron is localized in the bottom dot, so we need to consider only the hole configurations: Both holes can be in the top dot, both in the bottom dot, or one in each dot. The configuration with both holes in the top dot has a large Coulomb energy ($\Gamma^{(+)}$), because the holes are together and are separate from the electron. This puts its emission ~20 meV above the spectral range that we consider (*26*). On the other hand, the Coulomb energies of the other two configurations differ only by a small energy ($\Gamma^{(-)}$), which is the difference between the *e-h* attraction and *h-h* repulsion and amounts to a few meV. These two configurations are the initial states (black lines in Fig. 3A) that lead to our measured transitions.

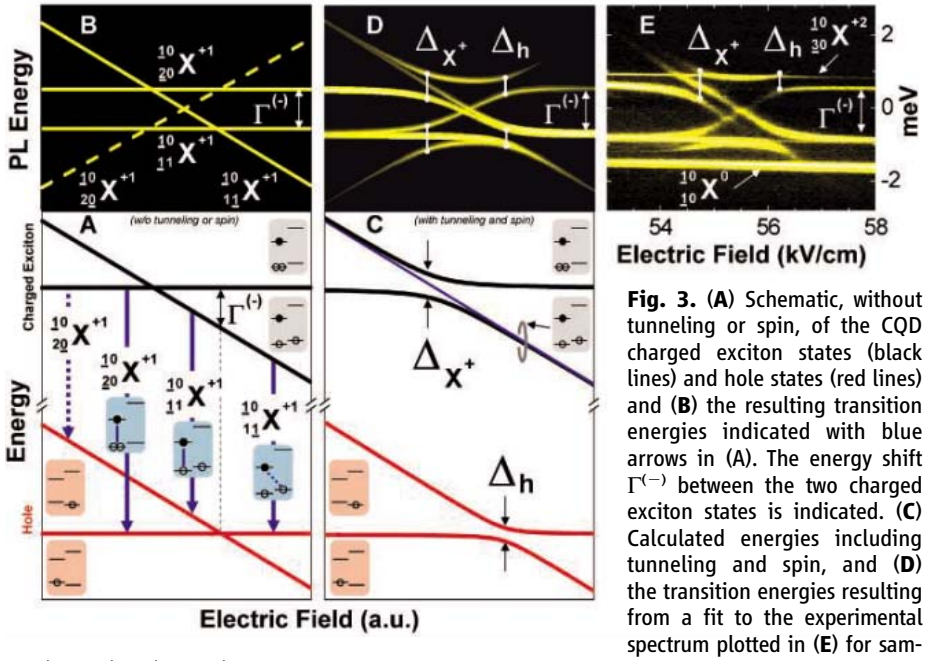

Fig. 3. (**A**) Schematic, without tunneling or spin, of the CQD charged exciton states (black lines) and hole states (red lines) and (**B**) the resulting transition energies indicated with blue arrows in (A). The energy shift $\Gamma^{(-)}$ between the two charged exciton states is indicated. (**C**) Calculated energies including tunneling and spin, and (**D**) the transition energies resulting from a fit to the experimental spectrum plotted in (**E**) for sample ($h_B/d/h_T$) = (4/4/2.5). With the introduction of tunneling and spin effects, we can see the two anticrossings events (Δ_h, Δ_{X^+}) which, along with $\Gamma^{(-)}$, give rise to the signature X-shape pattern. The parameters used to fit the data in (E) were $\Gamma^{(-)}$ = 1.27 meV and $t = 1/2(\Delta_h)$ = 0.23 meV. In (E), we note the two additional PL lines arising from the uncharged exciton ($^{10}_{10}X^{0}$) and the doubly positively charged exciton ($^{10}_{30}X^{+2}$). a.u., arbitrary units.

The Coulomb energy shift ($\Gamma^{(-)}$) between the two charged exciton states is the essential origin of the X-shape in the PL spectrum (Fig. 3B). With two charged exciton states and two hole states, we have four PL transitions—two direct ($^{10}_{20}X^{+1}$, $^{10}_{11}X^{+1}$) and two indirect ($^{10}_{11}X^{+1}$, $^{10}_{20}X^{+1}$). The indirect transition, $^{10}_{20}X^{+1}$, is normally forbidden because both holes of the charged exciton are in a different dot than the final state hole. The direct PL transitions are separated by $\Gamma^{(-)}$, and the indirect transitions cross midway between them (Fig. 3B).

To add the effects of tunneling to this simple model, we have calculated the energies of the states and the resulting optical spectrum of asymmetric pairs of InGaAs/GaAs quantum dots having one electron and two holes (*26*). The

calculated energies are shown in Fig. 3C and the corresponding calculated spectrum in Fig. 3D. We have calculated the strength of the transitions using the matrix elements and assuming that the initial states are thermally distributed. Because of tunneling, we find that the transition $^{10}_{20}X^{+1}$ becomes partially allowed. Moreover, tunneling produces delocalized molecular states only near the two fields where anticrossing is observed.

An important consequence of this energy level structure is that the molecular resonances for the hole and the charged exciton occur at different electric fields. This fact implies that there is a field where coupling between dots occurs only in the presence of optical excitation.

The inclusion of spin in the model leads to the identification of triplet states in the spectra. The $^{10}_{20}X^{+1}$ emission results when both holes are in the *s*-shell of the same dot, where they must be in a spin singlet configuration, just as with a SQD. However, when the two holes are in separate dots, both singlet and triplet configurations arise. This is similar to the situation found in measurements of electron transport through double dots (*8*–*10*). Because tunneling (mainly) conserves spin (*29*), anticrossings will occur only for states with identical spin configurations, and the triplet states will not anticross with the singlet states. This results in a triplet state that passes through the anticrossing region unaltered (blue line in Fig. 3C) and appears as characteristic PL lines (Fig. 3D) that pass unaffected through the Δ_{X^+} anticrossing regions, providing a clear signature of a spin triplet. We also observe fine structure in the spectra that indicates the presence of exchange interactions. Our theoretical description incorporates these effects (*26*), although detailed comparison with our predictions requires further investigation.

Good agreement is found between the calculated spectrum (Fig. 3D) and the measured spectrum (Fig. 3E), providing support for our model of coherent hole tunneling in a charged quantum dot molecule. Within our model, only two fitting parameters are necessary to reproduce the six observed PL lines: the difference in direct Coulomb energies ($\Gamma^{(-)}$) and the hole tunneling rate (t). Changing barrier thickness should lead to changes in the tunneling rate and the Stark shift of the indirect transition. We show that this is true in Fig. 4 for samples with barrier thicknesses of d = 6, 4, and 2 nm. Although the overall spectral pattern remains similar, we observe an obvious decrease in the slope (Stark shift) of the indirect PL line and an increase in the anticrossing energies, as expected. Although we find a large distribution of the anticrossing energies (e.g., for d = 6 nm, values of Δ_h vary from 0.23 to 0.55 meV), they show a systematic increase with decreasing barrier thickness. The values of $\Gamma^{(-)}$, however, range from 1 to 5 meV, with little obvious dependence on barrier thickness. This presumably arises from microscopic variations in structure (e.g., alloy composition, strain, etc.) but is not yet understood.

Comparing the anticrossing energies of the hole (Δ_h), the neutral exciton (Δ_{X^0}), and the charged exciton (Δ_{X^+}) reveals subtleties of the hole tunneling process. From these we obtain, respectively, the tunneling rate of the hole by itself (t), in the presence of an electron, or in the presence of an *e*-*h* pair. The anticrossing energy of the hole is $\Delta_h = 2t$. For X^0, with an extra electron, it is increased to $\Delta_0 = 2(t + \delta_0)$, where δ_0 is an *e*-*h* Coulomb correction (*26*). For X^+, with an additional *e*-*h* pair, we obtain $\Delta_{X^+} = 2\sqrt{2}(t + \delta_+)$, where δ_+ is the correction to the Coulomb interaction between the hole and the extra *e*-*h* pair and is partially canceled and reduced with respect to δ_0. However, the overall rate is increased by $\sqrt{2}$ because now two holes can tunnel. From the CQD spectrum shown in Fig. 2, we measure $(\Delta_h, \Delta_{X^0}, \Delta_{X^+})_{4nm}$ = (0.60, 0.84, 0.89) meV, implying a tunneling rate of t = 0.3 meV and Coulomb corrections (δ_0, δ_+) = (0.12, 0.02) meV.

We have shown that molecular resonance is achieved at different electric fields for the optically excited (trion) states and the ground (hole) states. This demonstrates that it is possible to bias the CQD so that the individual dots are not coupled except during optical excitation—potentially an important observation, because it provides the opportunity to use optical resonance to couple two dots only during the duration of an ultrashort laser pulse.

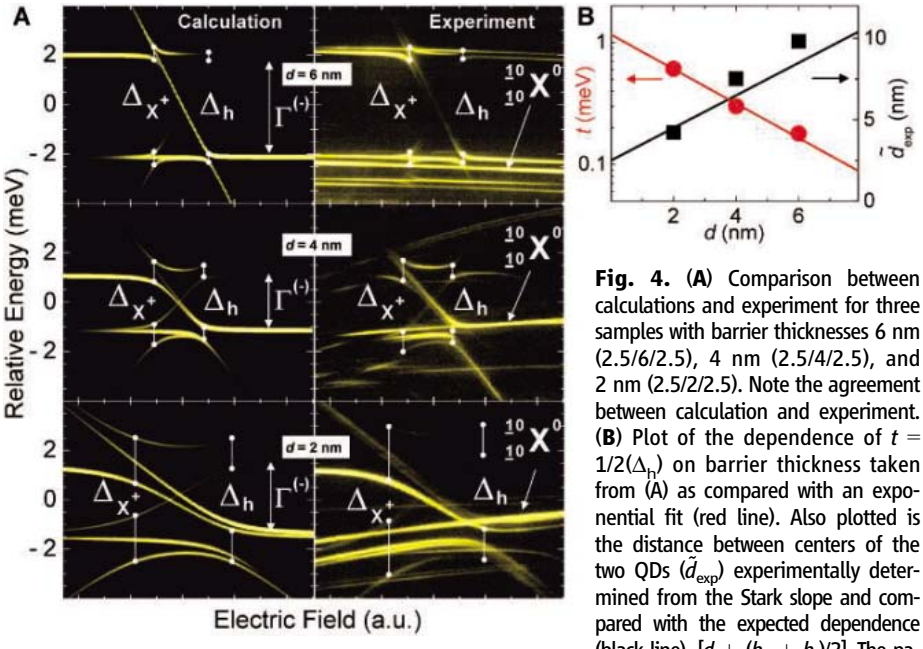

Fig. 4. (**A**) Comparison between calculations and experiment for three samples with barrier thicknesses 6 nm (2.5/6/2.5), 4 nm (2.5/4/2.5), and 2 nm (2.5/2/2.5). Note the agreement between calculation and experiment. (**B**) Plot of the dependence of $t = 1/2(\Delta_h)$ on barrier thickness taken from (A) as compared with an exponential fit (red line). Also plotted is the distance between centers of the two QDs ($\tilde{d}_{exp}$) experimentally determined from the Stark slope and compared with the expected dependence (black line), $[d + (h_B + h_T)/2]$. The parameters used in the calculations were taken from the following measured values: $(\Delta_h, \Delta_{X^+}, \Gamma^{(-)})_{6nm}$ = (0.36, 0.70, 4.17) meV, $(\Delta_h, \Delta_{X^+}, \Gamma^{(-)})_{4nm}$ = (0.60, 0.89, 2.24) meV, and $(\Delta_h, \Delta_{X^+}, \Gamma^{(-)})_{2nm}$ = (1.22, 2.26 2.97) meV. a.u., arbitrary units.

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29. This is only approximate; asymmetric *h*-*h* and *e*-*h* exchange will mix slightly the singlet and triplet states. Recently, it has been shown in electronic manipulation of charged molecules that hyperfine interactions can flip

electronic spin (*8*–*10*); however, unlike electrons, holes should not have strong hyperfine interactions.

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Plasticization-Enhanced Hydrogen Purification Using Polymeric Membranes

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Polymer membranes are attractive for molecular-scale separations such as hydrogen purification because of inherently low energy requirements. However, membrane materials with outstanding hydrogen separation performance in feed streams containing high-pressure carbon dioxide and impurities such as hydrogen sulfide and water are not available. We report highly permeable, reverse-selective membrane materials for hydrogen purification, as exemplified by molecularly engineered, highly branched, cross-linked poly(ethylene oxide). In contrast to the performance of conventional materials, we demonstrate that plasticization can be harnessed to improve separation performance.

Hydrogen is produced primarily by steam reforming of hydrocarbons followed by the water-gas shift reaction, which yields a hydrogen product containing impurities such as CO_2, H_2S, and H_2O (*1*). The hydrogen must be purified for further use, and based on the high volumes currently produced and the likelihood for this production to increase, even a small improvement in H_2 purification efficiency could substantially reduce the costs. Membrane technology is attractive for molecular-scale separations because of inherent advantages such as high energy efficiency, excellent reliability, and a small footprint (*2*–*5*). The potential applicability of membrane technology relies strongly on the ability of membrane materials to exhibit high separation performance at practical feed conditions (e.g., with feed streams that contain high-pressure CO_2 and impurities such as H_2S and H_2O).

Highly permeable and highly selective membrane materials are desired for CO_2/H_2 separation. Gas permeability P, which is the steady-state, pressure- and thickness-normalized gas flux through a membrane, is usually expressed as $P = S \times D$, the product of gas solubility S and gas diffusivity D in the polymer membrane (*6*). Selectivity $\alpha_{A/B}$, which characterizes the ability of a membrane to separate gases A and B, is given by

$$\alpha_{A/B} = \frac{P_A}{P_B} = \frac{S_A}{S_B} \times \frac{D_A}{D_B} \qquad (1)$$

where S_A/S_B is the solubility selectivity and D_A/D_B is the diffusivity selectivity (*6*). The selectivity of CO_2 over H_2, α_{CO_2/H_2}, reflects the tradeoff between favorable solubility selectivity (CO_2 is more condensable than H_2 and, therefore, $S_{CO_2}/S_{H_2} > 1$) and unfavorable diffusivity selectivity (CO_2 is larger than H_2, so $D_{CO_2}/D_{H_2} < 1$) (*7*). In conventional polymeric membrane materials (*8*) and those based on carbon (*4*) and silica (*9*, *10*), overall gas selectivity is dominated by diffusivity selectivity and, therefore, these materials are typically more permeable to H_2 than to CO_2. Consequently, the H_2 product is produced in the permeate at low pressure, even though further downstream utilization requires H_2 at high pressure. Expensive recompression of the H_2 product hence diminishes the advantage of membrane technology relative to that of conventional separation technologies, such as pressure swing adsorption, that produce H_2 at or near feed pressure (*1*, *2*, *6*). To minimize or avoid H_2 recompression, optimal membrane materials should be reverse selective (i.e., more permeable to larger molecules, such as CO_2, than to smaller molecules, such as H_2). Here, we propose that to achieve very high CO_2/H_2 selectivity, a membrane must exhibit favorable interactions with CO_2 to enhance solubility selectivity and have very weak size-sieving ability to bring D_{CO_2}/D_{H_2} as close to 1 as possible. Guided by these material design principles, we prepared and characterized a family of highly branched polymers based on poly(ethylene oxide) (PEO) and found that these polymers display excellent CO_2/H_2 separation performance. Counterintuitively, the CO_2/H_2 selectivity and CO_2 permeability improve as CO_2 partial pressure increases (i.e., as CO_2 concentration sorbed in the polymer increases). This is in contrast to the behavior of conventional, strongly size-selective materials, for which raising CO_2 partial pressure typically decreases selectivity (*11*).

In a recent review of the influence of primary chemical structure on CO_2/H_2 separation properties of polymers, ethylene oxide (EO) units were identified as the best chemical groups for such membranes because the polar ether oxygens in EO units interact favorably with CO_2, resulting in high solubility selectivity (*12*). Polymers containing EO can be highly flexible, leading to weak size-sieving behavior and high diffusion coefficients, two factors which contribute directly to high CO_2 permeability and high CO_2/H_2 selectivity (*12*, *13*). However, pure PEO exhibits very low CO_2 permeability [approximately 12 Barrers (*14*) at 35°C and infinite dilution] as a result of high crystallinity levels (*7*). Additionally, the presence of crystalline regions in pure PEO reduces polymer chain mobility in the amorphous phase and increases size-sieving ability, thereby decreasing CO_2/H_2 selectivity (*12*). To circumvent this limitation and effectively frustrate crystallization, short non-PEO segments are introduced into the polymer backbone to interrupt the EO repeat units. Chain branches containing short, noncrystallizable segments of EO are also introduced randomly into the chain backbone to further inhibit crystallinity. This leads to amorphous materials with higher gas permeability and higher CO_2/H_2 selectivity than semicrystalline PEO. Plasticization further improves their CO_2/H_2 separation properties, in contrast to the view that plasticization always reduces polymer membrane separation performance, as it does in the case of CO_2/CH_4 separation in natural gas purification (*15*). Moreover, all polymers are more permeable to CO_2 than to CH_4 because CO_2 has higher diffusivity (because of its smaller molecular size) and higher solubility (because of its greater tendency to condense) than CH_4. In contrast, polymers that are more permeable to CO_2 than to H_2 are much rarer because the smaller size of H_2 favors its permeation over that of the larger CO_2.

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Our family of amorphous, high-molecular-weight, cross-linked, network copolymers was synthesized by photopolymerizing different composition ratios of poly(ethylene glycol) diacrylate [PEGDA: CH_2=CHCOO(CH_2CH_2O)$_{14}$OCCH=CH_2] and poly(ethylene glycol) methyl ether acrylate [PEGMEA: CH_2=CHCO(OCH_2CH_2)$_8$$OCH_3$] (*16*, *17*). The resulting copolymer network has the general chemical structure shown in Fig. 1. PEGDA contains EO units in its backbone, and PEGMEA has pendant EO units. Cross-linked copolymer samples with 0 to 99 weight percent (wt %) PEGMEA and the balance PEGDA were prepared and characterized. Independent of the concentration of PEGDA and PEGMEA, the copolymers contain about 82 wt % EO. Increasing PEGMEA content increases fractional free volume and, in turn, CO_2 permeability and pure-gas CO_2/H_2 selectivity. However, at low temperatures (≤0°C), materials with very high PEGMEA content (e.g., 91 wt %) crystallize, resulting in a substantial permeability decrease below 0°C. We extensively investigated the CO_2/H_2 permeation properties of the 70 wt % PEGMEA/30 wt % PEGDA copolymer at –20°, 10°, and 35°C with pure gases and three binary CO_2/H_2 mixtures of different compositions (*16*). We chose this temperature range not only because this copolymer does not crystallize over this range but also because this range is consistent with the operating temperature of some industrial processes currently used for H_2 purification (*1*). Additionally, to determine the effect of H_2O and H_2S impurities on CO_2/H_2 separation properties, the 91 wt % PEGMEA/9 wt % PEGDA copolymer was characterized at 22°C with a moisture-laden CO_2/H_2 mixture and a four-component, H_2S-containing gas mixture that mimicked the composition of process synthesis gas. In both pure- and mixed-gas studies, the PEGMEA/PEGDA films were physically stable at transmembrane pressure differences up to 21 atm (the maximum value explored in our study), and their gas permeability coefficients were independent of previous thermal and gas exposure history, as expected for rubbery polymers. Permeability coefficients were independent of film thickness, which varied from 70 to 500 μm.

Figure 2 shows the dependence of CO_2 and H_2 permeability coefficients on CO_2 partial pressure in the feed at different temperatures. As CO_2 partial pressure increases, CO_2 and H_2 permeabilities increase at all temperatures; the permeability rise is greater at lower temperatures because of higher CO_2 thermodynamic activity (at a fixed partial pressure) in the polymer film at cooler temperatures. Both pure- and mixed-gas permeabilities also follow the same trends, suggesting that the permeability increase is in large measure a result of increasing CO_2 partial pressure. As indicated by an increase in CO_2 diffusivity with increasing CO_2 concentration in the film (*18*), CO_2 sorbed in the polymer plasticizes the polymer chains, leading to an increase in fractional free volume and, in turn, gas permeability. With decreasing temperature, CO_2 sorption and, hence, plasticization increase so that the effect of CO_2 partial pressure on permeability becomes even stronger.

Decreasing temperature typically decreases gas permeability as a result of a reduction in polymer chain mobility and, therefore, diffusivity at lower temperatures (*6*, *19*). However, Fig. 2A demonstrates that decreasing temperature does not necessarily decrease CO_2 permeability, especially at high CO_2 partial pressure. For example, at a CO_2 feed partial pressure of 17 atm, the CO_2 permeability at –20°C is 410 Barrers, which is higher than that at 10°C (300 Barrers) and very similar to that at 35°C (440 Barrers). Thus, the permeability decrease that would normally accompany a temperature reduction is essentially offset by the increase in CO_2 solubility and the increased plasticization of the polymer by CO_2, which increases diffusivity at lower temperatures.

Decreasing temperature considerably increases mixed-gas CO_2/H_2 selectivity. As shown in Fig. 3, at a CO_2 partial pressure of 17 atm, mixed-gas selectivity increases from 9.4 to 31 as temperature decreases from 35° to –20°C. Furthermore, the selectivity of 31 is accompanied by a CO_2 permeability of 410 Barrers, which is orders of magnitude higher than that observed in conventional polymer membranes used for CO_2 separations (*6*). Facilitated transport membranes can exhibit high CO_2/light gas selectivity at low CO_2 partial pressure (~1 atm or less); however, the selectivity in these materials decreases strongly as CO_2 pressure increases (*20*–*22*). Such materials are often studied for low CO_2 partial pressure applications (e.g., removal of CO_2

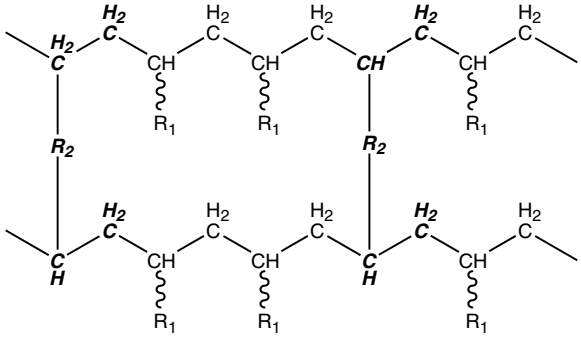

Fig. 1. Schematic representation of PEGDA/PEGMEA copolymer network. Italicized and bolded parts of the network derive from the cross-linker. R_1 is $CO(OCH_2CH_2)_8OCH_3$ from PEGMEA; R_2 is $COO(CH_2CH_2O)_{14}OC$ from PEGDA.

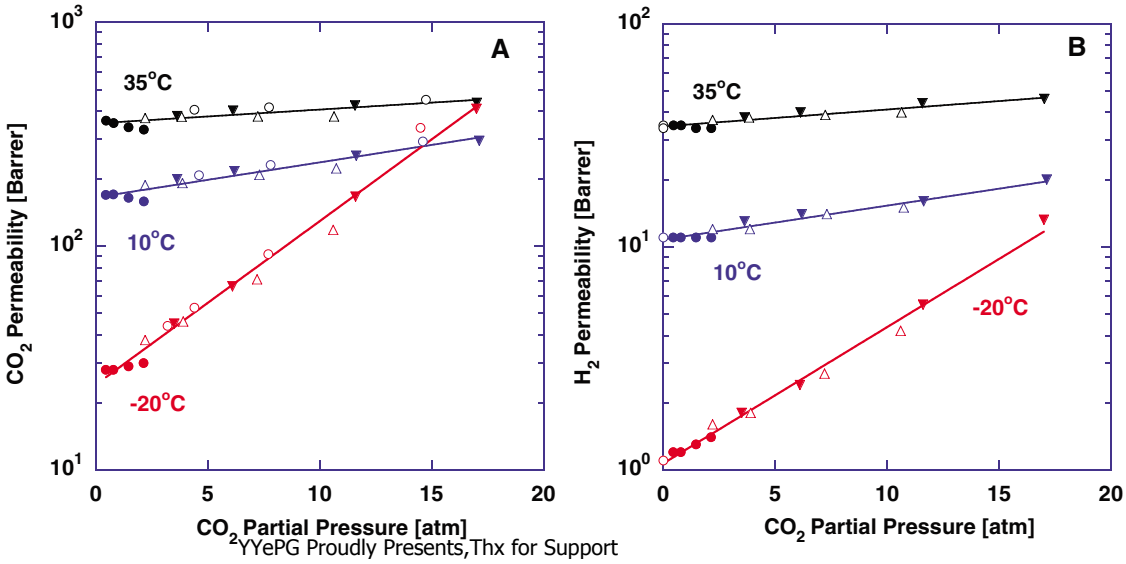

Fig. 2. Effect of temperature and CO_2 upstream partial pressure on (**A**) pure- and mixed-gas CO_2 permeability and (**B**) pure- and mixed-gas H_2 permeability in 70 wt % PEGMEA/30 wt % PEGDA copolymer (*14*). Pure-gas permeability data are shown as open circles (○). Mixed-gas CO_2/H_2 feed compositions (in mol % CO_2:mol % H_2) were 10:90 (●), 50:50 (Δ), and 80:20 (▼). Uncertainty in the permeability data was ±10% or less. The lines are provided to guide the eye.

from breathing gas aboard spaceships (*20*). However, they cannot operate at the high pressures required for hydrogen applications because they are often based on liquids supported in porous media, and the liquids typically cannot be maintained in the porous support when a large pressure difference is applied across the membrane (*23*, *24*).

Mixed-gas selectivity is essentially independent of CO_2 partial pressure at 35° and 10°C (Fig. 3). However, as CO_2 partial pressure increases at –20°C, mixed-gas CO_2/H_2 selectivity increases by 35%. In conventional size-sieving polymers, plasticization of the polymer by CO_2 or other condensable components results in mixed-gas selectivity values that decrease, often markedly, as CO_2 partial pressure increases (*11*) or when other strongly sorbing impurities such as higher hydrocarbons are present (*25*). For example, when the CO_2 partial pressure increased from 1 to 10 atm, the CO_2/CH_4 selectivity of a rigid, glassy, strongly size-sieving, aromatic polyimide decreased from 40 to about 4 (*11*).

We ascribe the mixed-gas CO_2/H_2 selectivity results for the PEGMEA/PEGDA copolymers to the inherent transport properties of these reverse-selective materials (*3*, *26*). At high CO_2 partial pressures, these materials sorb considerable amounts of CO_2, leading to swelling and an increase in free volume, which presumably decreases the glass transition temperature (T_g) (*27*–*29*) and weakens the size-sieving ability of the membrane (*26*).

Figure 4 presents a permeability/selectivity map for CO_2/H_2 separation. The upper bound line in the figure gives an estimate of the highest pure-gas selectivity possible for a given permeability in polymer-based materials at 25°C (*8*). Unlike separation based on strong size-sieving ability [where there is a strong tradeoff between permeability and selectivity (*8*, *30*)], the positive slope of the upper bound indicates that high CO_2 permeability and high CO_2/H_2 selectivity may be achieved simultaneously. The PEGMEA/PEGDA copolymers we explored exhibit excellent separation performance for CO_2/H_2 mixtures, and decreasing temperature actually moves the CO_2/H_2 separation performance above the upper bound line. However, because this line is commonly established by permeation properties of polymers at or near 25°C (*8*), the upper bound may shift as temperature deviates from 25°C. Currently, there is no model to predict the temperature dependence of the upper bound, and there are not yet enough systematic experimental data available to provide clear evidence of its temperature dependence.

The effect of impurities such as H_2O and H_2S on CO_2/H_2 separation properties was investigated at 22°C with the 91 wt % PEGMEA/9 wt % PEGDA copolymer. Although this material crystallizes at about 0°C, it is wholly amorphous at the experimental temperature studied. Because it contains more PEGMEA, this copolymer is more permeable than the 70 wt % PEGMEA/30 wt % PEGDA material presented in Figs. 2 to 4. At 25°C, the infinite-dilution CO_2 permeability is 380 Barrers for the 91 wt % PEGMEA copolymer and 280 Barrers for the 70 wt % PEGMEA material. The addition of 0.33 mole percent (mol %) H_2O vapor (i.e., 100% relative humidity) to a feed gas containing a 1:3 mixture of CO_2:H_2 at 22°C and a feed pressure of 8.0 atm increased CO_2 permeability of the 91 wt % PEGMEA copolymer from 360 to 515 Barrers and its mixed-gas CO_2/H_2 selectivity from 7.8 to 12. We ascribe this change to plasticization by H_2O, which tends to improve CO_2/H_2 separation performance by a mechanism probably very similar to that by which higher CO_2 partial pressure increases CO_2/H_2 selectivity.

The 91 wt % PEGMEA copolymer was also evaluated with a four-component gas mixture composition representative (on a dry basis) of a synthesis gas stream produced by a commercial General Electric (formerly, Texaco) quench gasifier (*31*). This mixture contained 1.0% H_2S, 12.5% CO_2, and 35.7% H_2 in CO. The separation of H_2S from H_2, similar to that of CO_2 from H_2, requires reverse-selective membrane materials with weak size-sieving ability and a polar nature to interact more favorably with this acid gas. At a feed pressure of 7.8 atm, the copolymer had an H_2S permeability of 2500 Barrers and a mixed-gas H_2S/H_2 selectivity of 50. H_2S is considerably more soluble than CO_2 in polar polymers (*32*, *33*), and this effect contributes to the much higher H_2S permeability than CO_2 permeability in the material. Additionally, CO_2 permeability and CO_2/H_2 selectivity remain unchanged in the presence of H_2S, indicating the robustness of this series of polymers for CO_2/H_2

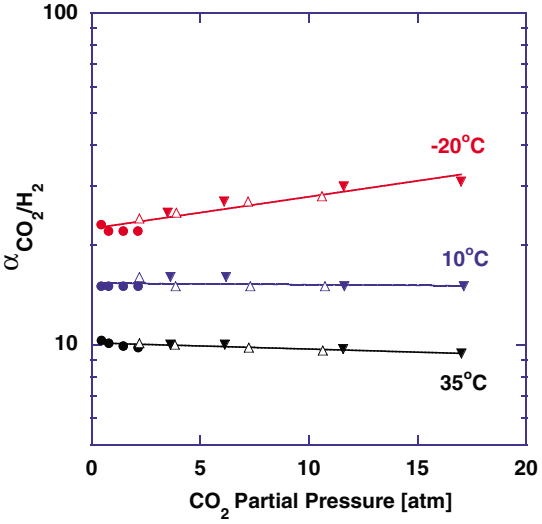

Fig. 3. Effect of CO_2 partial pressure and temperature on mixed-gas CO_2/H_2 selectivity (α_{CO_2/H_2}) in 70 wt % PEGMEA/30 wt % PEGDA copolymer. Mixed-gas CO_2/H_2 feed compositions (in mol % CO_2:mol % H_2) were 10:90 (●), 50:50 (Δ), and 80:20 (▼). The lines are provided to guide the eye.

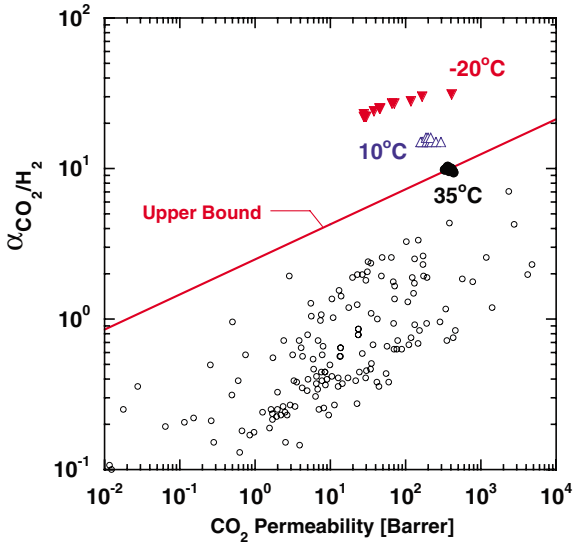

Fig. 4. Permeability/selectivity map for CO_2/H_2 separation. Mixed-gas separation performance data of the 70 wt % PEGMEA/30 wt % PEGDA copolymer at 35°C (●), 10°C (Δ) and –20°C (▼) are included for comparison. The various symbols at each temperature represent data points measured at different feed pressures and binary CO_2/H_2 mixture compositions. Each open circle on the graph represents the separation characteristics of a different material from the literature. Data at lower CO_2 permeability correspond to lower CO_2 partial pressures in the feed gas and vice versa. The upper bound is drawn according to a model prediction of this phenomenon (*30*) with the adjustable parameter f set to 0. The parameter f characterizes the interchain spacing at equilibrium. Rubbery polymers such as those of interest in this work do not exhibit the nonequilibrium excess volume that is associated with nonzero values of f in glassy polymers.

separation. If the H_2S partial pressure were higher, it might sorb to high enough levels to alter the gas transport properties of the polymer.

In summary, a family of reverse-selective membrane materials based on highly branched, cross-linked PEO exhibits outstanding separation performance for H_2 purification by removing acid gases such as CO_2 and H_2S from feed streams of practical interest. Moreover, the presence of moisture and high-pressure CO_2 in the feed actually improves permeability and selectivity, in contrast to the detrimental behavior associated with plasticizing agents in conventional membrane materials. In addition to hydrogen purification applications, these molecularly engineered copolymers may also be used to remove CO_2 and H_2S from natural gas as well as SO_2 and NH_3 from nonpolar gases.

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Asymmetric Hydrogenation of Unfunctionalized, Purely Alkyl-Substituted Olefins

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Asymmetric hydrogenation of olefins is one of the most useful reactions for the synthesis of optically active compounds, especially in industry. However, the application range of the catalysts developed so far is limited to alkenes with a coordinating functional group or an aryl substituent next to the double bond. We have found a class of chiral iridium catalysts that give high enantioselectivity in the hydrogenation of unfunctionalized, trialkyl-substituted olefins. Because these catalysts do not require the presence of any particular functional group or aryl substituent in the substrate, they considerably broaden the scope of asymmetric hydrogenation.

Asymmetric hydrogenation is one of the most widely used, most reliable catalytic methods for the preparation of optically active compounds (*1*–*3*). High enantioselectivity, low catalyst loadings, essentially quantitative yields, and mild conditions are attractive features of this transformation. Since the early 1970s, when the well-known L-DOPA (L-dioxyphenylalanine) process was established at Monsanto (*3*), hydrogenation has played a dominant role in industrial asymmetric catalysis (*4*). An enormous variety of chiral phosphine ligands has been developed, many of which induce very high enantioselectivity in rhodium- and ruthenium-catalyzed hydrogenations.

However, despite great progress during recent decades, the range of olefins that can be hydrogenated with high enantiomeric excess (ee) is still limited. Both rhodium and ruthenium catalysts require the presence of a polar functional group next to the C=C bond, which can coordinate to the metal center. Hydrogenation of dehydro–amino acid derivatives or allylic alcohols are typical examples. With unfunctionalized olefins, these catalysts generally show low reactivity and unsatisfactory enantioselectivity. Therefore, their application is restricted to certain classes of properly functionalized substrates.

Some years ago, we introduced iridium complexes with chiral P,N ligands (ligands with coordinating P and N atoms) as catalysts that overcome these limitations (Fig. 1) (*5*–*19*). Various unfunctionalized aryl-substituted olefins can be hydrogenated with high enantioselectivity and high catalytic efficiency using catalysts of this type. Nonetheless, satisfactory

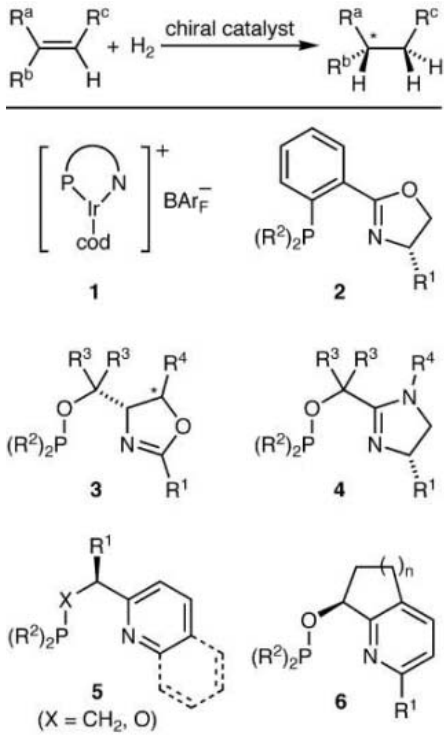

Fig. 1. Asymmetric hydrogenation of olefins with iridium catalysts **1** derived from chiral ligands **2** to **6**. Abbreviations: cod, cycloocta-1,5-diene; BAr_F, tetrakis[bis-3,5-(trifluoromethyl)phenyl]borate.

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results in the hydrogenation of purely alkyl-substituted olefins have been elusive. Absent the need for any specific functional group or aryl substituent, the reaction could be applied to a much wider range of useful substrates.

Originally, we focused our work on oxazoline-based P,N ligands such as **2** and **3** (*5*–*7*), but more recently we have extended the ligand spectrum to derivatives containing an imidazoline ring (**4**) (*10*, *11*) or a pyridine or quinoline ring in combination with a chiral backbone (**5**) (*8*) (Fig. 1). In view of the promising results obtained with pyridine-phosphinites of type **5** (X = O), we prepared a series of bicyclic analogs **6**; we expected the more rigid geometry imposed by the additional ring to raise enantioselectivity (*20*). Iridium complexes derived from five- and six-membered ring derivatives **6** (n = 1, 2) proved to be efficient catalysts, inducing enantioselectivities generally higher than those of the analogous ligands **5**. Here, we report that certain derivatives of these ligands can induce high enantioselectivity in the hydrogenation of purely alkyl-substituted olefins.

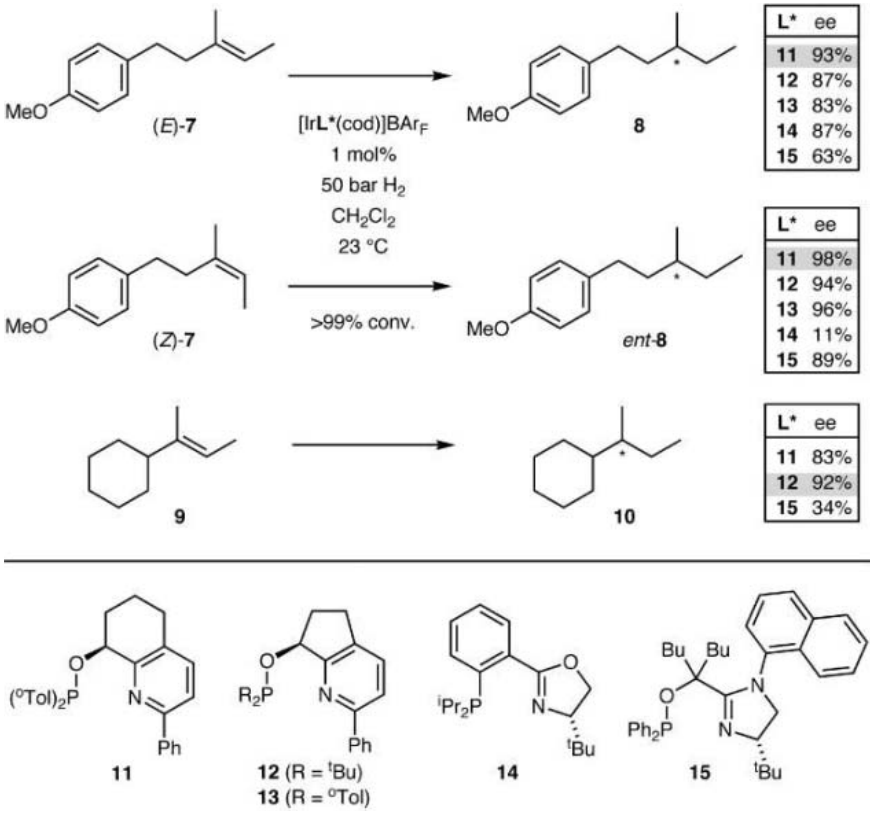


Fig. 2. Asymmetric hydrogenation of trialkyl-substituted olefins. Abbreviations: °Tol, *o*-tolyl; Bu, *n*-butyl; tBu, *tert*-butyl; iPr, isopropyl; Me, methyl; Ph, phenyl. Products **8** and *ent*-**8** are enantiomers (*30*). Stereogenic centers in the products are marked by asterisks; L* denotes the chiral ligand used, and the shaded bars highlight the best result for each catalyst.

Initially, we used the (*E*)- and (*Z*)-olefins **7** as test substrates (Fig. 2) (*21*). The methoxyphenyl group was introduced to facilitate product analysis, because the enantiomers of pure hydrocarbons are difficult to separate by gas chromatography (GC) or high-performance liquid chromatography (HPLC) on chiral columns. Although an interaction of the remote aryl group with the iridium catalyst could not be excluded, we expected that such an interaction would be weak, and therefore that these substrates would be good models for purely alkyl-substituted olefins. Most ligands that had given high enantioselectivities with alkenes containing an aryl substituent at the C=C bond performed poorly with (*E*)- and (*Z*)-**7**. Pyridine-based ligands **11**, **12**, and **13** were exceptions, giving full conversion and ee values between 83 and 98% (*21*, *22*). Among a series of oxazoline- and imidazoline-derived ligands, two derivatives **14** and **15** induced reduction with almost 90% ee. However, these two ligands performed well only with one of the substrate isomers. The best enantioselectivities were obtained with the bicyclic pyridine-phosphinite ligand **11**, giving 93% and 98% ee for the (*E*)- and the (*Z*)-isomer, respectively. Consistent with previous studies (*6*), the (*E*)- and (*Z*)-isomers were converted to products of opposite configuration.

These results encouraged us to search for a suitable substrate devoid of any heteroatom or aryl group but still allowing reliable determination of the enantioselectivity after hydrogenation. Cyclohexylalkene **9** was found to meet these requirements (Fig. 2). It was readily prepared in high isomeric purity (*E*/*Z* > 99:1) following published procedures (*23*, *24*), and the ee value of the hydrogenation product could be determined by GC on a chiral column (*21*). This substrate proved to be more demanding than alkenes (*E*)- and (*Z*)-**7**, and most ligands studied gave ee values below 30%. We identified only two ligands, the bicyclic pyridine-phosphinites **11** and **12**, that induced enantioselectivities of >80% ee. Nonetheless, the ee value of 92% obtained with ligand **12** shows that highly enantioselective hydrogenation of purely alkyl-substituted olefins is possible.

Hydrogenation of alkene **9** serves mainly as a proof of principle. However, the iridium catalysts shown in Fig. 2 could extend the range of synthetic strategies for accessing the many natural products or pharmaceutically important compounds with chiral alkyl fragments. Such structures should result efficiently from asymmetric hydrogenation of suitable

Fig. 3. Structures of the tocopherols, the principal components of vitamin E (*25*). In α-tocopherol, R^1 = Me, R^2 = Me; in β-tocopherol, R^1 = Me, R^2 = H; in γ-tocopherol, R^1 = H, R^2 = Me; in δ-tocopherol, R^1 = H, R^2 = H.

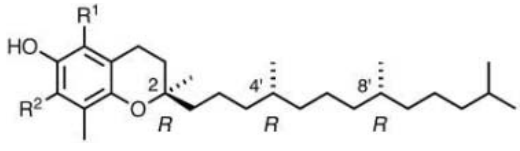
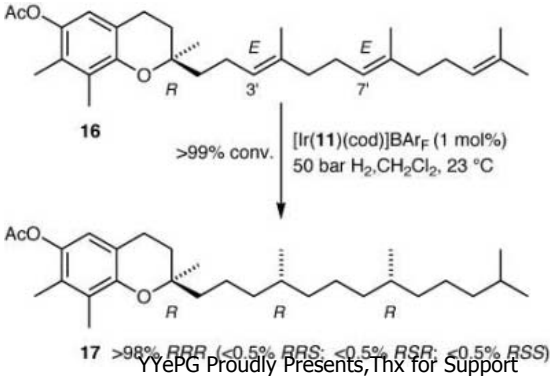


Fig. 4. Hydrogenation of γ-tocotrienyl acetate **16** (AcO, acetate).



alkene precursors. Moreover, if a precursor with more than one C=C bond were used, two or more stereogenic centers could be introduced in one step with absolute stereocontrol. Because (*E*)- and (*Z*)-olefins are converted to products of opposite configuration, the relative stereochemistry can be controlled by proper choice of the geometry of the individual C=C bonds.

In this way, to take one example, the stereocenters in the terpenoid side chain of tocopherols could be introduced stereoselectively (Fig. 3), providing an attractive route to these biologically and economically important fat-soluble antioxidants, which are the main components of vitamin E. Despite considerable effort in various laboratories, no commercially viable stereoselective total synthesis of (*RRR*)-tocopherols has been developed so far (*25*).

To demonstrate the potential of our catalysts for transformations of this type, we studied the hydrogenation of γ-tocotrienyl acetate **16** (Fig. 4). In this reaction, which involves hydrogenation of three C=C bonds, two new stereogenic centers are created and, therefore, four stereoisomers can be formed. Because the two prochiral double bonds are both (*E*)-configured, the sense of asymmetric induction at the two reaction sites is expected to be the same, leading either to the (*RR*)- or (*SS*)-configuration depending on the absolute configuration of the catalyst. The influence of the stereogenic center present in the substrate is very weak, as shown by hydrogenation with an achiral iridium catalyst [ligand **2** (R^1 = H, R^2 = Ph); face selectivity, 59:41 and 52:48 at the C(3′) and C(7′) double bond, respectively]. Determination of the isomeric composition of the hydrogenation product is difficult, but a suitable method has been described that involves GC analysis after conversion of the acetate **17** to the corresponding methyl ether (*26*, *27*).

We screened various iridium catalysts derived from ligands of types **2** to **6** (Fig. 1) in the hydrogenation of tocotrienol derivatives (*28*). Whereas oxazoline-based ligands showed disappointingly low stereoselectivities, imidazolines **4** and pyridine-phosphinites **6** gave encouraging results. The most efficient ligand in the imidazoline series was derivative (*R*)-**15**, producing a 90:5:4:1 mixture of (*RRR*)-, (*RRS*)-, (*RSR*)-, and (*RSS*)-tocopheryl acetates (*21*, *22*). However, the best stereoselectivity was achieved with the iridium catalyst derived from pyridine-phosphinite ligand **11**, which gave almost exclusively the natural (*RRR*)-isomer of γ-tocopheryl acetate **17** (*29*), thus providing a highly effective stereoselective route to this important class of bioactive antioxidants. Previously developed strategies for the stereoselective synthesis of vitamin E compounds (*25*) use a stepwise approach for the introduction of the stereogenic centers in the side chain. Here, the natural *RR* configuration is established in a single step.

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30. The absolute configuration of the products has not yet been determined. The ee values are based on HPLC (product **8**) and GC analysis (**10**) using chiral columns (*21*).

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Plastic Deformation of $MgGeO_3$ Post-Perovskite at Lower Mantle Pressures

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Polycrystalline $MgGeO_3$ post-perovskite was plastically deformed in the diamond anvil cell between 104 and 130 gigapascals confining pressure and ambient temperature. In contrast with phenomenological considerations suggesting (010) as a slip plane, lattice planes near (100) became aligned perpendicular to the compression direction, suggesting that slip on (100) or (110) dominated plastic deformation. With the assumption that silicate post-perovskite behaves similarly at lower mantle conditions, a numerical model of seismic anisotropy in the D″ region implies a maximum contribution of post-perovskite to shear wave splitting of 3.7% with an oblique polarization.

The D″ region, the layer above the core-mantle boundary (CMB), exhibits a seismic discontinuity, substantial seismic anisotropy, and considerable lateral heterogeneity, and it plays a key role in our understanding of the deep Earth (*1*–*4*). Seismic anisotropy in D″ could reflect lattice preferred orientation (LPO) of minerals (*5*) or alignment of structural elements, including layers of melt (*6*, *7*). LPO patterns depend on deformation mechanisms, and interpretation of D″ anisotropy has been ambiguous because of the absence of any experimental constraints on such properties. Here, we report results of an experimental study of deformation of $MgGeO_3$ post-perovskite (pPv) at high pressures.

Post-perovskite is the stable phase of $MgSiO_3$ at D″ pressures and is likely to be one of the main constituents of D″ (*8*–*14*). First-

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principles calculations indicate that it has a strong elastic anisotropy (*9*, *15*–*17*), and experimental results show that the *b* axis is more compressible than the *a* and *c* axes (*8*). On the basis of structural considerations, pPv has been suggested to form platy crystallites parallel to (010) (fig. S1) or needle-like crystallites in the direction of [100], and (010) has been suggested as the dominant slip plane (*8*, *9*, *15*). In contrast, first-principles calculations indicate that C_{66} is larger than C_{44} and C_{55}, which is incompatible with the concept of a layered structure parallel to (010) (*16*). More recent calculations have also identified a family of polytypes intermediate between Pv and pPv and suggest (110) as a dominant slip plane (*18*).

We deformed a sample of polycrystalline $MgGeO_3$-pPv plastically in the diamond anvil cell between 104 and 130 GPa, heating to 1600 K in different cycles, and observed the evolution of LPO in the sample in situ using radial x-ray diffraction (*19*). Germanates have long been regarded as suitable low-pressure analogs for silicates, based on crystal chemistry systematics and the similarity of slip systems (*20*–*22*). $MgGeO_3$ exhibits nearly the same transition sequence as $MgSiO_3$ with increasing pressure, including a transition to a pPv phase at about 63 GPa (*23*). $MgGeO_3$-pPv also displays a strong elastic anisotropy (*23*). The transition pressure to the pPv phase in $MgGeO_3$ is almost half that of $MgSiO_3$ (120 GPa), and the diffraction intensity of $MgGeO_3$ is greater than $MgSiO_3$. Therefore, $MgGeO_3$ is a good candidate for experimental investigation of plasticity of pPv phases under deep mantle pressures.

We performed an angle dispersive radial x-ray diffraction experiment (fig. S2) at the High-Pressure Collaborative Access Team (HPCAT) sector of the Advanced Photon Source (beamline 16-ID-B). Starting material was a powder of pure $MgGeO_3$ orthopyroxene mixed with 10 weight percent Pt powder that served as pressure calibrant and laser absorber. It was compressed to a pressure of 104 GPa and then converted into the pPv phase by laser heating in different locations at a temperature of 1600 K for about 10 min. Pressure was then increased to 124 GPa over 5 hours. At this stage, the sample was left for 15 hours to allow relaxation of stresses and strains. Later, the sample was further heated for about 20 min at 1600 K and left for 18 hours to allow relaxation. At the end of this cycle, pressure in the sample was on the order of 130 GPa (table S1). At every step, we collected radial diffraction patterns to evaluate the pressure, stress, and LPO in the sample (*24*).

The diffraction images show substantial variations of diffraction peak positions and intensities with orientation relative to the compression direction (Fig. 1) that can be used to estimate stress and deduce LPO. We analyzed the x-ray diffraction images with two different methods (*24*): One relies on individual peak fitting (*19*), and the other relies on a full image analysis with the Rietveld method (*25*). The differential stress in the $MgGeO_3$-pPv sample ranged from 3.6 to 8.9 GPa and evolved continuously with increasing pressure (table S1). The texture we obtained is represented as inverse pole figures of the compression direction in Fig. 2. We observed a texture with a maximum between (100) and (110) at 104 GPa that did not change with time, further heating, or further compression. At 104 and 130 GPa, the ODF maximums were 1.89 and 1.96 multiples of a random distribution, respectively (table S1). A distinct minimum was at (010). Results from individual peak fitting (Fig. 2B) and the Rietveld method (Fig. 2C) were similar.

To interpret the observed textures, we simulated the development of LPO in pPv polycrystals deformed by slip in compression using a viscoplastic self-consistent (VPSC) polycrystal plasticity model (*26*). The LPO evolution depends on the imposed deformation history and the active slip systems. At this point, little is known about deformation mechanisms in pPv. Therefore, we decided to investigate several combinations of slip systems and critical resolved shear stresses for (100), (010), (001), and (110) (table S2). In agreement with predictions of first-principles calculations suggesting (110) as slip plane in pPv (*18*), the best match with experiments was obtained for simulations with dominant slip on (100), (110), or a combination of the two (Fig. 2, D and G), indicating that those are the most likely slip planes at the conditions of the experiment. Slip on (010) and (001) did not produce a maximum near (100), and slip on (010) produced a maximum rather than the observed minimum at (010) (Fig. 2, E and F). A comparison between the strength of the experimental and calculated textures indicates that the macroscopic compressive strain was 0.2 in the experiment.

There are limitations in using analogs to extract meaningful rheological properties at temperature, stress, and strain rate conditions that are far removed from those in the earth. However, assuming that (100) and (110) slip also applies to $MgSiO_3$-pPv under deep mantle

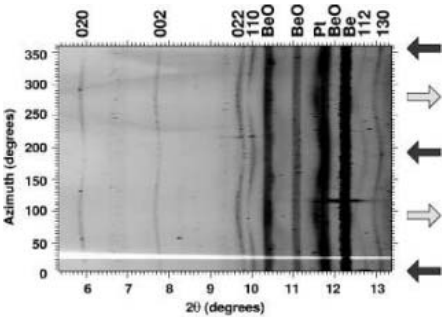

Fig. 1. Unrolled diffraction image of $MgGeO_3$ measured in radial geometry, in situ, at 130 GPa. The directions of maximum and minimum stress are indicated by the black and gray arrows, respectively. LPO and deviatoric stress are deduced from the variations of diffraction intensity and peak position with orientation. Diffraction peaks from the $MgGeO_3$ sample, Pt pressure calibrant, and Be and BeO from the gasket material are labeled on the figure. Because of the geometry of the experiment, Be and BeO peaks always appear as double lines.

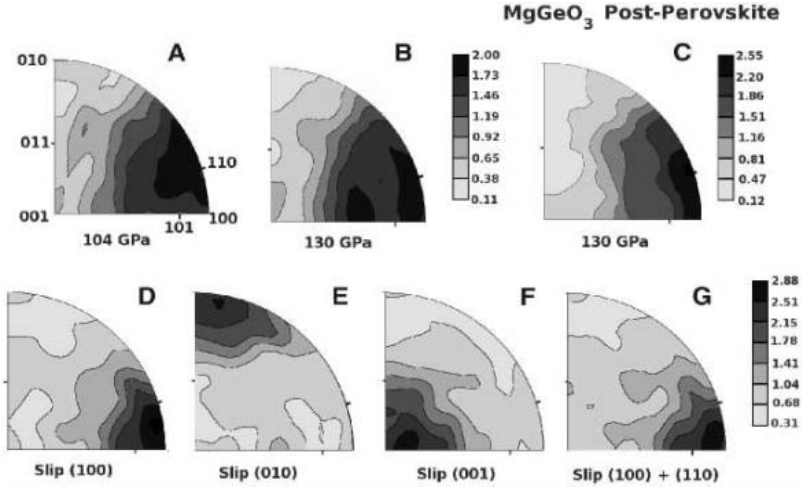

Fig. 2. Inverse pole figure showing the preferred orientation pattern in $MgGeO_3$ pPv in compression measured (**A**) at 104 GPa just after converting the material to the pPv phase; (**B**) at 130 GPa, 41 hours later, after cycles of laser heating and pressure increase, calculated using the individual peak fitting method; (**C**) at 130 GPa, calculated using the Rietveld method; and (**D** to **G**) simulated after 20% compressive strain with models that favor slip along (100), (010), (001), and both (100) and (110), respectively. Equal-area projection is used, and linear contours are expressed in multiples of random distribution.

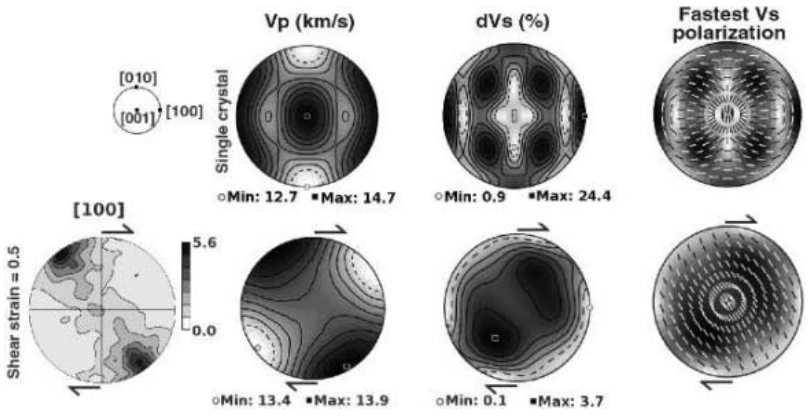

Fig. 3. Modeled three-dimensional compressional velocities (V_P), shear wave splitting (dV_S), and fastest shear wave polarization at 135 GPa and 4000 K for $MgSiO_3$ pPv single crystal (top row) and for a polycrystal aggregate (bottom row) after simple shear plastic deformation up to a strain of 0.5, along with the corresponding [100] pole figure. Linear scale, equal-area projection. Contours for [100], V_P, and dV_S pole figures are expressed in multiples of a random distribution, kilometers per second, and percentage, respectively. Black and white lines (for low and high anisotropy, respectively) in right panel indicate the direction of polarization of the fast shear wave.

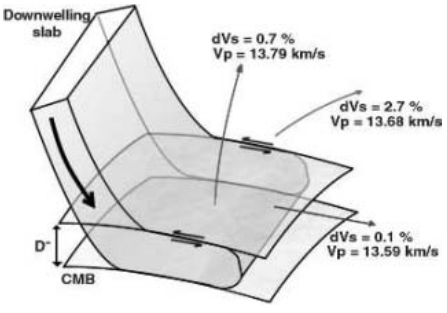

Fig. 4. Contribution of silicate-pPv to anisotropy in a region deformed in simple shear parallel to the CMB.

conditions, we obtained an estimate of expected anisotropies in the D″ layer using again VPSC polycrystal plasticity models to calculate the three-dimensional orientation distribution and then average the single-crystal elastic tensors as a function of crystallographic orientation. From the aggregate elastic tensor, we then calculated seismic velocities in different directions. As a typical deformation path for shear zones, we used simple shear to an equivalent strain of 0.5, corresponding to a shear $\gamma = 0.86$, and slip system combinations that favor slip on (100) and (110). For such a model, the [100] axes tend to align in an oblique maximum rotated from the shear plane normal against the direction of shear (Fig. 3).

The single-crystal anisotropy calculated at 135 GPa and 4000 K (*17*) for *P* waves is 15% (Fig. 3), and shear wave splitting (dV_S) reaches 24%, but the pattern is complex. The polycrystal average for simple shear deformation displays a weak directional anisotropy of only 3.4% for *P* waves and a maximum of 3.7% for shear wave splitting. The relatively low anisotropy is related to the complex single-crystal elastic tensor where maxima and minima are superposed during averaging. For *S* waves, the largest amount of splitting occurs at an inclination of about 45° from both the plane and direction of shear.

Seismological observations have reported large delays for shear waves that graze horizontally through the D″ region with shear wave splitting delays of up to 10 s, corresponding to a polarization anisotropy of up to 3% in D″. These observations have also shown that the anisotropy style—$V_{SH} > V_{SV}$, $V_{SH} < V_{SV}$ (where V_{SH} and V_{SV} are the velocities of the horizontally and vertically polarized shear waves, respectively), or tilted transverse anisotropy—varies regionally (*2*, *4*, *27*–*29*). For a region in which deformation occurs in simple shear parallel to the CMB, we found that the contribution of pPv to shear wave splitting should range from 0.1 to 3.1% for waves traveling in the plane of shear (Fig. 4). In agreement with recent seismic observations of tilted transverse anisotropy in D″ (*28*, *29*), we also found that for silicate pPv the polarization anisotropy is usually inclined by about 45° compared with the plane of shear.

These results underline the importance of high-pressure experimentation in assessing plasticity and seismic anisotropy in the deep Earth. In the future, this work will have to be complemented with experiments on silicate pPv itself, higher temperatures, and lower strain rates.

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Natural and Experimental Evidence of Melt Lubrication of Faults During Earthquakes

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Melt produced by friction during earthquakes may act either as a coseismic fault lubricant or as a viscous brake. Here we estimate the dynamic shear resistance (τ_f) in the presence of friction-induced melts from both exhumed faults and high-velocity (1.28 meters per second) frictional experiments. Exhumed faults within granitoids (tonalites) indicate low τ_f at 10 kilometers in depth. Friction experiments on tonalite samples show that τ_f depends weakly on normal stress. Extrapolation of experimental data yields τ_f values consistent with the field estimates and well below the Byerlee strength. We conclude that friction-induced melts can lubricate faults at intermediate crustal depths.

How large is τ_f of faults during earthquakes? Although it is a crucial parameter for understanding the dynamics of seismic rupture, τ_f is virtually inaccessible to seismological methods (*1*–*3*). The interpretation of seismological and geophysical data suggests that many ruptures occur as self-healing pulses (*4*) and that dynamic stress drops are larger than static stress drops (*1*, *5*). Increases in heat flow have not been found near active faults (*6*). These observations can be explained by low τ_f (*4*, *7*). Melt lubrication is a possible cause of low τ_f (*8*–*11*), because solidified, clast-laden, friction-induced melts (pseudotachylytes) decorate some exhumed ancient faults (*12*). However, evidence of melt is not ubiquitous on faults, indicating that other weakening mechanisms may be important, especially in the presence of fluids (*13*–*15*). In addition, a high-viscosity melt might act as a viscous brake, damping seismic slip instead of lubricating (*2*, *11*, *16*, *17*).

Here we estimate τ_f from large exposures of pseudotachylyte-bearing faults and through the experimental production of friction melt on samples from the same natural rock that produced the pseudotachylyte in the fault exposures. Both field and experimental data coherently indicate melt lubrication and low fault strength during earthquakes.

Assuming that most frictional work during faulting is converted into heat (i.e., the energy associated with the creation of new surfaces is negligible) (*2*, *18*), it is possible to determine τ_f from natural pseudotachylytes (*12*). Indeed, if the volume of the pseudotachylyte per unit fault surface, w (in meters), and the displacement d (in meters) accommodated by the fault to produce the melt are known, then (*10*)

$$\tau_f = \rho\left[(1 - \phi)H + c_p(T_i - T_{hr})\right]w/d \quad (1)$$

where $\rho = 2700$ kg m^{-3} is the rock density, $\phi = 0.2$ is the volume ratio of lithic clasts within the pseudotachylyte, $H = 3.28 \times 10^5$ J kg^{-1} is the latent heat of fusion, $c_p = 1180$ J kg^{-1} K^{-1} is the specific heat at constant pressure at 1300 K, and $(T_i - T_{hr}) = 1200$ K is the difference between initial melt temperature and host rock temperature. These values are appropriate for the exhumed strike-slip Gole Larghe fault zone, which crosscuts tonalites of the Adamello batholith (Italian Alps) (*10*, *19*). The fault zone is exposed in glacier-polished outcrops and is composed of about 200 major subparallel faults.

The fault rocks predominantly consist of an association of cataclasites overprinted by pseudotachylytes (*19*). In most of the observed faults, part of the cumulative slip has been accommodated without the production of pseudotachylytes; in such cases, it is not possible to apply Eq. 1. However, a few faults are delineated by pseudotachylyte alone. Pseudotachylytes are distributed along the fault surface and fill injection veins that intrude the host tonalite (Fig. 1, A and B). In these faults, the absence of a precursor cataclasite is confirmed by optical and scanning electron microscope (SEM) investigations. It appears that locally, pseudotachylyte formed during a single seismic rupture that propagated through intact tonalite. The displacement d along these single-event faults was determined from the measured separation of dikes, xenoliths, and mylonites crosscut by the faults (*19*). The volume of the pseudotachylyte per fault surface unit, w, was determined in two ways in

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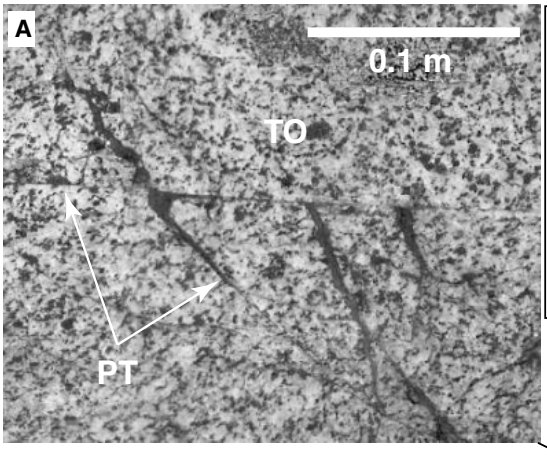

C

Outcrop	Fault displ. mm	PT thickn. mm	Thickn./ displ.	Shear stress MPa
Lobbia 2000_1*	120	0.5	0.0042	18.9
32 _ 2003*	250	2.0	0.0080	36.3
Lobbia 2000_2*	340	1.5	0.0044	20.0
Lobbia 2000_3*	500	2.0	0.0040	18.1
P058 35m vs N*	610	2.0	0.0033	14.9
Lobbia 2000_4*	660	7.0	0.0106	48.1
P040 10m vs N*(AM)	790	6.9	0.0087	39.6
A14_2004 (AM)	1440	5.9	0.0041	18.6

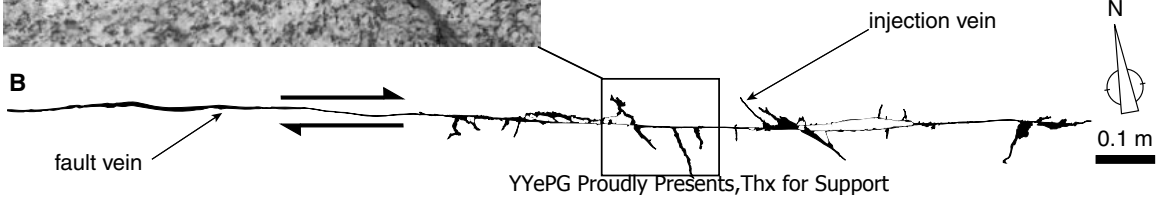

Fig. 1. Field example of pseudotachylyte. (**A**) Pseudotachylytes (PT, black color) decorate the main fault and are locally injected into the tonalitic (TO) host rock. (**B**) Fault profile of a pseudotachylyte-bearing fault. Note the variation in thickness of the pseudotachylyte along strike. (**C**) Table of field data. Asterisks indicate data published in (*10*); AM, area method. Dynamic shear stress τ_f was estimated from Eq. 1 using the ratio of observed PT thickness and fault offset.

outcrops orthogonal to fault dip. For thin, continuous fault veins of constant thickness and free of injection veins, we measured w as the average pseudotachylyte thickness along the studied fault segment [following the method described by Sibson (*12*)]. For thick and complex pseudotachylyte-bearing vein networks (Fig. 1A), we determined w by dividing the outcrop area occupied by the melt (including the pseudotachylyte in the fault vein as well as in injection veins and dilation jogs) (Fig. 1B) for the length of the fault profile ("area method") (*10*). From the w/d values of single-event pseudotachylyte of the Gole Larghe Fault, Eq. 1 yields τ_f between 14.9 and 48.1 MPa (Fig. 1C).

In the Gole Larghe fault, seismic slip (pseudotachylyte production) occurred at temperatures of 250 to 300°C and at depths of 9 to 11 km (*20*). During faulting, a low pore fluid pressure can be assumed on the basis of several microstructural observations (*10*). On the other hand, the production of pseudotachylytes indicates relatively dry conditions, because the presence of fluids activates other weakening mechanisms (e.g., thermal pressurization by pore fluids) that might prevent the onset of bulk frictional melting (*13*). Assuming low fluid pressures and a stress tensor in agreement with strike-slip faulting (*10*, *21*), the effective stress normal to the fault at a depth of 10 km (for a rock density of 2600 kg m^{-3}) is between 112 MPa (hydrostatic pore pressure) (*10*) and 182 MPa (no pore pressure).

Four high-velocity rock friction experiments were conducted in a rotary shear apparatus (*22*). In each experiment, we used a pair of solid cylinders (22.3 mm in diameter and ~23 mm in length) of tonalite from the host rock of the Gole Larghe fault zone. A different normal load σ_n was applied during each experiment (5, 10, 15, and 20 MPa). The samples were subjected to a sudden step in rotation velocity from 0 rpm (velocity of 0 m s^{-1}) to 1500 rpm (which corresponds to an equivalent slip velocity of 1.28 m s^{-1}) (Fig. 2) (*22*). The imposed equivalent slip velocity is within the range of seismic slip rates (1 to 3 m s^{-1}) estimated for natural earthquakes (*1*, *2*, *4*). Specimens were jacketed with a 1-mm-thick aluminum ring to avoid sample destruction by thermal fracturing (*23*). This sample preparation allowed the application of σ_n up to 20 MPa, which is 1 order of magnitude larger than in previous shear melting experiments (*22*, *24*). The area of the aluminum ring in contact with the sliding surface was rapidly consumed because of the relatively low melting temperature of aluminum (660°C), compared with that of the dominant tonalite-forming minerals [>1000°C (*25*, *26*)]. Under the relatively high applied σ_n, runs lasted from 4 to 8 s and displacements reached a few meters, in contrast with the several tens of seconds and tens of meters achieved during previous studies (*22*, *24*). The durations of our experiments are comparable to the typical rise time of large earthquakes (*2*, *4*).

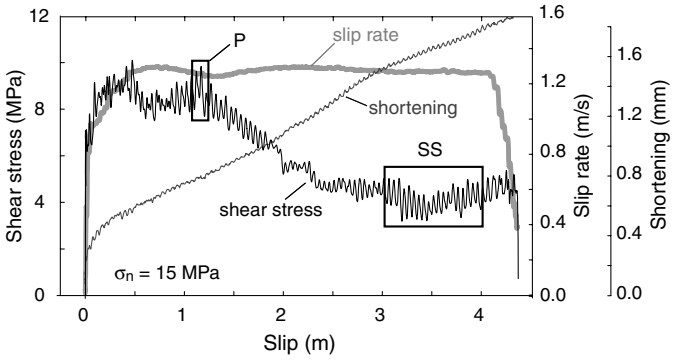

Fig. 2. Experimental results for tonalite at a slip rate of 1.28 m s^{-1} and normal stress of 15 MPa. Boxes P and SS indicate the displacement intervals used to determine peak and steady-state shear stress, respectively, plotted in Fig. 4A.

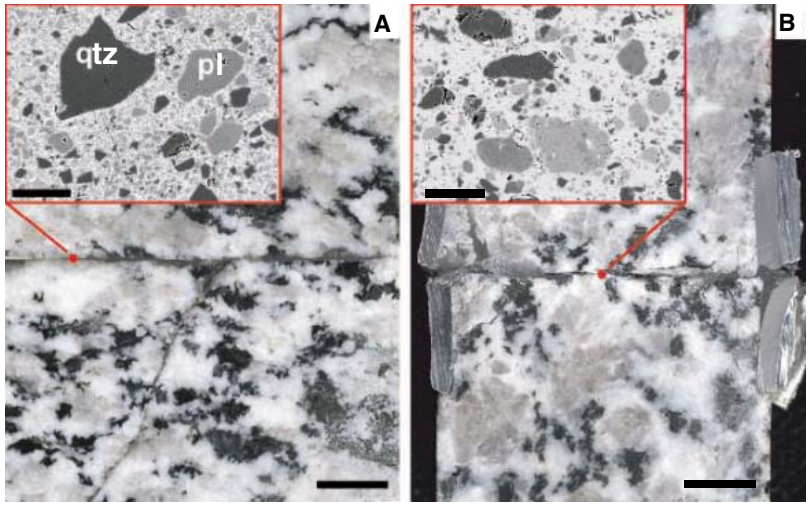

Fig. 3. Comparison between (**A**) natural and (**B**) experimental pseudotachylyte. The insets are SEM back-scatter images of the pseudotachylyte (inset scale bars, 50 μm). Pseudotachylytes consist of quartz (qtz) and plagioclase (pl) clasts suspended within a biotite (bright white) microlitic matrix in natural pseudotachylyte (A) or in a glassy matrix in artificial pseudotachylyte (B). In (B), the aluminum external ring is bent toward the outside and separated by a thin but continuous melt layer. The bulge to the right is epoxy. Scale bars, 5 mm.

During the experiments, friction-induced melt was produced along the sliding surface and largely extruded from the sample assembly. Such melt extrusion resembles what happens in natural faults, where most of the melt has been injected from the sliding surface of the fault where it was produced (i.e., fault vein) into lateral veins (i.e., injection veins) or pull-apart regions (Fig. 1, A and B). Some melt still remained along the sliding surface at the end of the experiment, and this remaining melt formed a continuous layer of artificial pseudotachylyte that resembled natural pseudotachylytes of the Gole Larghe fault (Fig. 3). Pseudotachylyte consists of quartz and plagioclase clasts immersed in a microlitic (natural pseudotachylyte) (Fig. 3A) or glassy (artificial pseudotachylyte) (Fig. 3B) matrix. Microlites are absent in artificial pseudotachylytes, because the cooling of the melt to laboratory room temperature (20°C) is more rapid than in the Gole Larghe fault, where the host rock temperature was 250 to 300°C (*20*).

During the experiments, the shear stress increased up to a peak value achieved after ~1.0 m of sliding (Fig. 2, box marked P). This initial fault strengthening reflects the formation and shearing of discontinuous melt patches between the rock surfaces (*22*). After the peak value, the shear stress gradually decreased (transient stage), usually over 1 to 2 m of slip, toward a steady-state shear stress (Fig. 2, box marked SS). Melt was squeezed out from the specimen throughout the experiment, starting from the transient stage (*26*). During the steady-state stage, the specimen shortened at a constant rate of ~0.5 mm s^{-1} as melt was produced and evacuated (Fig. 2). Thus, steady-state shear stress is achieved in the presence of the following: (i) a continuous film of melt wetting the sliding surface (Fig. 3B) and (ii) steady evacuation of melt, confirmed by the constant shortening rate of the sample.

In a viscous regime, defining the standard friction coefficient as $\mu = \tau_f/\sigma_n$—as in the case

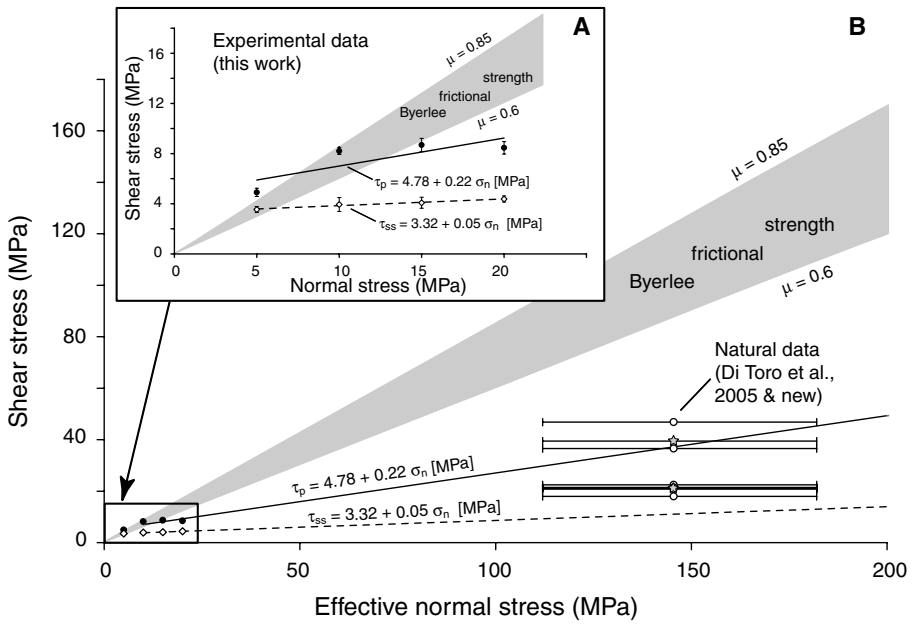

Fig. 4. Shear stress versus effective normal stress for (**A**) experimental data and (**B**) natural data, compared with Byerlee's frictional strength for tonalite. Solid circles and open diamonds are experimental values for peak shear stress and steady-state shear stress (Fig. 2), respectively; open circles and open stars are field data estimates according to Eq. 1. Open stars indicate estimates by means of the area method. Experimental data have vertical error bars (SD) due to the slight oscillations in shear stress with displacement (Fig. 2). Field data have a large range of effective normal stress (as indicated by the horizontal error bars) due to the poorly constrained pore pressure at the time of seismic faulting. The solid line is the best linear fit for the peak shear stress data; the dashed line is the best linear fit for the steady-state shear stress data. Most field data lay within the dynamic shear strength curves extrapolated from the experimental data, well below Byerlee's friction curves (plotted in gray as a reference for $0.6 < \mu < 0.8$).

of solid friction—is misleading (*11*, *22*). Instead, we represent τ_f as a function of σ_n, and the simple form $\tau_f = \alpha + \mu_{eff}\,\sigma_n$ reasonably fits the data, where α is the intercept at zero normal stress and μ_{eff} is an effective friction coefficient (Fig. 4A). For peak shear stress (black line), $\tau_f = 4.78 + 0.22\sigma_n$ (in MPa), whereas for steady-state shear stress (dashed line), $\tau_f = 3.32 + 0.05\sigma_n$ (in MPa). It appears that shear stress is weakly sensitive to σ_n, whereas in a purely viscous regime, resistance to slip is independent of the normal stress (*11*). In the studied natural faults, the sliding surfaces are wetted by a continuous melt layer, which is one of the two conditions satisfied during the steady-state stage in the experiments. However, the τ_f deduced for the natural faults is an average value integrated over the entire slip event (i.e., strengthening and weakening), so it is expected to lie between the peak and steady-state shear stress.

The best-fit curves for shear stress determined in the lab (Fig. 4A) have been extrapolated to crustal conditions at depths of 10 km and are in reasonable agreement with the field data (Fig. 4B). These findings show that shear strength is low in the presence of melts during seismic slip. The field data indicate that τ_f is lower than that for Byerlee's frictional strength (*27*). The experimental data also indicate that τ_f is low and has a slight dependence on normal stress. This is a clear deviation from Byerlee's law (Fig. 4A) and suggests melt lubrication. Overall, the experimental and field estimates of τ_f follow nearly the same dynamic strength curve, indicating good agreement between laboratory and field data and that dynamic fault strength is well below that assumed for a typical Byerlee's frictional law.

Although the abundance of pseudotachylytes in nature is still a debated issue, friction-induced melts are easily produced in the laboratory. The effects of melt lubrication on the fault surface must be considered in some earthquake rupture models.

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26. The friction-induced melt appears after ~0.5 m of sliding, and it is squeezed out from the sliding surface because of the large σ_n exerted (Movie S1). At this initial stage, the aluminum rings were already weakened and bent toward the outside by the starting melt extrusion (Fig. 3B). We conclude that the aluminum rings were not in contact during the experiment—with the exception of the initial sliding phase—and mechanical data are not affected by the frictional strength of the external aluminum ring. This was confirmed by specimen investigation after the experiments, which showed that the two opposite aluminum rings were separated by a thin and continuous tonalitic melt layer (Fig. 3B). Other experiments indicated that the selected shape of the sample (solid instead of hollow shaped) did not affect the mechanical data, because peak and steady-state shear stress are similar for both type of specimens, although shear stress versus displacement curves might be slightly different (fig. S1), as discussed in (*11*).
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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5761/647/DC1
Fig. S1
Movie S1

5 October 2005; accepted 30 December 2005
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Evolution of a Polyphenism by Genetic Accommodation

Yuichiro Suzuki* and H. Frederik Nijhout

Polyphenisms are adaptations in which a genome is associated with discrete alternative phenotypes in different environments. Little is known about the mechanism by which polyphenisms originate. We show that a mutation in the juvenile hormone-regulatory pathway in *Manduca sexta* enables heat stress to reveal a hidden reaction norm of larval coloration. Selection for increased color change in response to heat stress resulted in the evolution of a larval color polyphenism and a corresponding change in hormonal titers through genetic accommodation. Evidently, mechanisms that regulate developmental hormones can mask genetic variation and act as evolutionary capacitors, facilitating the origin of novel adaptive phenotypes.

Polyphenisms, such as the castes of social insects, the solitary and gregarious phases of migratory locusts, and the winged and wingless forms of aphids, are evolved adaptations to a varying environment (*1*–*3*). The adaptive importance of polyphenisms has been demonstrated in many cases, and many studies have shown that the threshold for the switch between alternative phenotypes can evolve in response to external selective pressures (*4*–*9*). Although much work has been done on the evolutionary maintenance of polyphenisms and the evolutionary shifts of polyphenic thresholds (*10*, *11*), little is known about the evolutionary and developmental mechanism behind the origin of these threshold traits.

We tested the hypothesis that a polyphenism can evolve through genetic stabilization of a stress-induced phenotype, a process known as genetic assimilation (*2*). Because related species are likely to share genetic and developmental backgrounds, we reasoned that exposing hidden genetic variation by stress (*12*) may allow us to evolve a polyphenic regulatory mechanism in a monophenic species that shares a recent common ancestor with a polyphenic species. We studied this possibility by evolving a larval color polyphenism in the tobacco hornworm, *Manduca sexta*, a monophenic species with green larvae (*13*); a related species, *M. quinquemaculata,* exhibits a larval color polyphenism, developing a black phenotype at 20°C and a green phenotype at 28°C (*14*). Because thermal stress is commonly encountered in the wild (*15*), we chose to use temperature stress to obtain phenocopies (*16*).

Wild-type larval coloration was robust to thermal stress, with the fifth instar larva remaining green after heat shock during the mid and late fourth larval instar. We also examined the effect of thermal stress in the *black* mutant line of *M. sexta*. The *black* mutation is a sex-linked recessive allele that reduces juvenile hormone (JH) secretion (*17*), which results in an increased melanization of the larval epidermis. The black mutant phenotype can be rescued by treatment with JH (*17*), yielding a normal green-colored larva. Larvae of the *black* mutant are black at physiologically tolerable temperatures ranging from 20°C to 28°C (fig. S2). Heat shocks during the sensitive period of the fourth larval instar generated fifth instar larvae with colors that ranged from normal black to nearly normal green, with the majority showing a slight color change (Fig. 1 and fig. S2). The *black* strain was most sensitive to a 6-hour heat shock applied less than 8 hours before apolysis (the detachment of the epidermis from the cuticle, which is the first step in the molting process), at the molt from the fourth to the fifth larval instar (fig. S1).

The diversity of heat shock–induced phenotypes provided us with a range of phenotypic variants upon which we could artificially select. We established two lines: one selected for increased greenness upon heat treatment (polyphenic line), the other for decreased color change upon heat treatment (monophenic line). About 300 larvae were reared and heat-shocked every generation, and approximately 60 with the most desirable phenotypic response were selected to establish the subsequent generation. An unselected control line was heat-shocked every generation to monitor any change that was not a direct result of selection. The response to selection (Fig. 2A) shows that the induced color change is heritable. The variation in the phenotype is continuous rather than discrete, which indicates that the induced color change is under polygenic control. The monophenic line lost its response to temperature shock after about the seventh generation of selection and remained black thereafter, with little phenotypic response to heat shock.

The reaction norms of the three lines in the 13th generation are shown in Fig. 2B. The unselected control line has a narrow threshold between 30°C and 33°C, with the inflection point at 32.7°C. As a result of selection, two major evolutionary changes have taken place in the polyphenic line: (i) completely green coloration at lower temperatures of 28°C, not seen in the control line (fig. S2), and (ii) a threshold shift to a lower temperature with the inflection point at 28.5°C. The monophenic line remained black at all temperatures. Thus, selection resulted in the evolution of different phenotypes at different constant environmental temperatures (fig. S2) and changed the shape of the reaction norm (Fig. 2B) so that the response to a small temperature change in the transition region became more discrete, or switchlike.

The time of the sensitive period for heat shock corresponds to the time of the JH-sensitive period for epidermal color determination (*17*, *18*). Topical application of JH to unselected black mutant during this sensitive period reverses the black phenotype to the green wild-type color. Dopa decarboxylase (DDC), the enzyme that converts dopa to dopamine in the melanin synthesis pathway, is first synthesized about 16 hours after this sensitive period (*19*), which indicates that heat shock

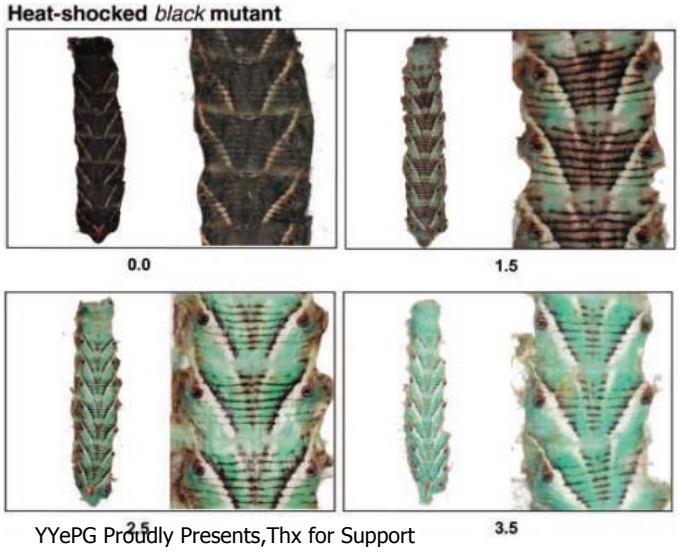

Fig. 1. The range of larval coloration observed in the heat-shocked larvae of the *black* mutant. The numbers below represent the scoring system used to quantify the color change: 0 is completely black, and 4 is completely green. Non–heat-shocked *black* mutant and non–heat-shocked wild-type larvae of *M. sexta* have the phenotypic scores of 0 and 4, respectively.

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affected an upstream regulatory control of melanin synthesis. Because JH and ecdysteroids have been implicated in the regulation of melanization (*19*) and because these hormones play a major role in the control of most insect polyphenisms (*18*), we determined whether the polyphenic and monophenic lines differed in the hormonal regulation of melanin synthesis. Hormones are secreted from either the prothoracic glands in the thorax (e.g., ecdysone) or the brain and corpora allata in the head (e.g., JH). A blood-tight ligature across the body of the larvae allows us to investigate which hormones might be involved (Fig. 3A). When the ligature was placed behind the first abdominal segment, the anterior compartment of larvae from the polyphenic line changed color upon heat shock, but the posterior compartment did not (Fig. 3B and fig. S3). The monophenic line remained black both anterior and posterior to the ligature (Fig. 3C and fig. S3). When the ligature was placed behind the neck, no color change response to heat shock was observed in either line, indicating that a cue from the brain/corpora allata was required for the color change (fig. S4).

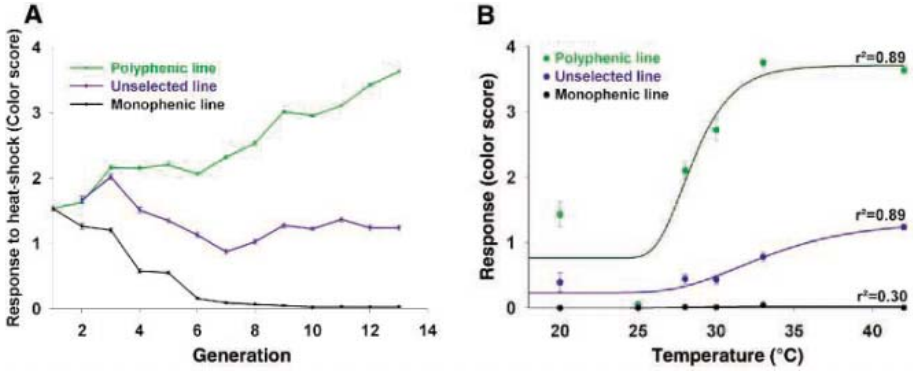

Fig. 2. Effect of selection on temperature-mediated larval color change. (**A**) Changes in the mean coloration of heat-shocked larvae in response to selection for increased (green) and decreased (black) color response to heat-shock treatments, and no selection (blue). (**B**) The reaction norm of generation 13 lines reared at constant temperatures between 20°C and 33°C, and heat-shocked at 42°C. The curves are sigmoidal regressions on the mean data points. Error bars represent 1 SE.

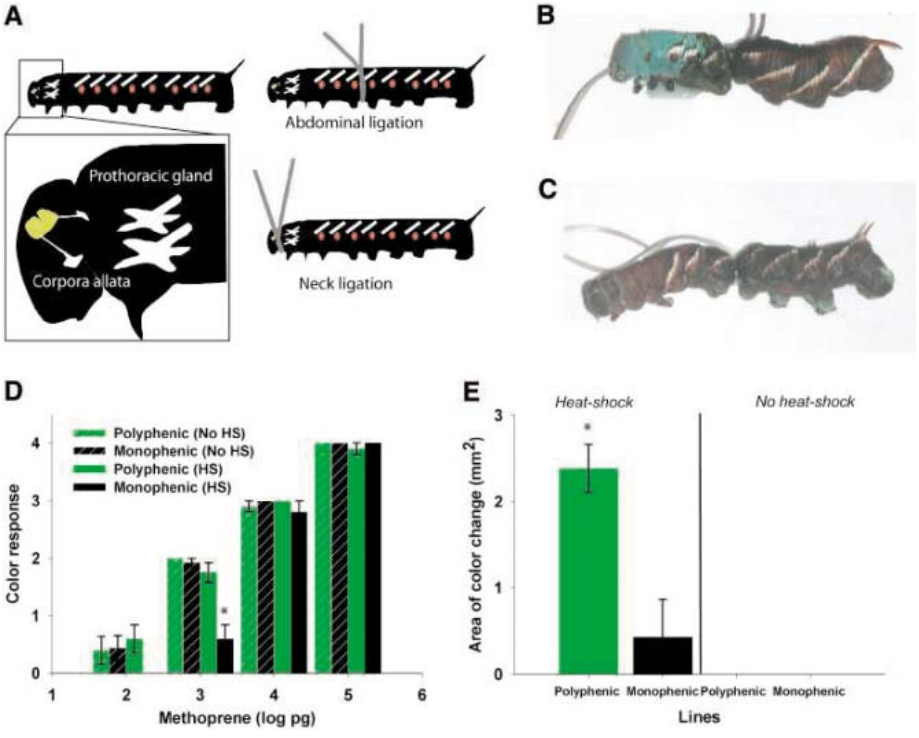

Fig. 3. The hormonal control in larvae of the polyphenic and monophenic lines. (**A**) Abdominal and thoracic ligations result in the exclusion of both corpora allata (secretes JH) and prothoracic gland (secretes ecdysone) posterior to the ligation. Neck ligation results in the exclusion of only the corpora allata posterior to the ligation. (**B** and **C**) Heat-shocked, ligated larvae from the polyphenic (B) and monophenic (C) lines. (**D**) Effect of methoprene treatment on thoracically ligated larvae of the polyphenic (green bars) and monophenic (black bars) lines with (filled) and without (diagonal) heat shock (HS). (*$P < 0.0001$ compared with non–heat-shocked monophenic line). (See table S2 for raw data.) (**E**) Results from the JH bioassay. The area of color change reflects the dose of hemolymph JH in polyphenic (green bars) and monophenic (black bars) larvae (*$P < 0.001$ compared with heat-shocked monophenic line). Error bars represent 1 SE. Statistical significance is based on a two-tailed Student's *t* test.

We compared the JH titers of the two lines during the sensitive period using a JH bioassay (*20*). The results show that polyphenic larvae, when heat-shocked, had higher JH titer during the critical period than did monophenic larvae (Fig. 3E). Thus, selection for increased color change was accompanied by an increased JH titer during the heat shock.

Thus, changes in hormonal regulation may underlie the evolution of a larval color polyphenism. Our results provide an example of the quantitative genetic model for genetic accommodation (*3*). Genetic accommodation is a mechanism of evolution wherein a novel phenotype introduced through a mutation or environmental change is molded into an adaptive phenotype through quantitative genetic changes. Genetic accommodation differs from genetic assimilation in that the latter results in canalization of the new phenotype so that it is no longer affected by environmental variation, whereas genetic accommodation can result in an increased environmental sensitivity of a plastic phenotype (*3*). Because the *black* mutation was necessary to predispose the population to reveal genetic variants through heat shock, and the final result was an enhanced response to the environment, with alternative canalizations in different environments, genetic accommoda-

tion is the correct description of the observed results.

We present here a mechanistic view of the evolution of polyphenisms by genetic accommodation: First, a mutation in the hormonal regulatory pathway (the *black* mutation in the current study) lowers the hormonal titer in such a way that environmental variation can expose genetic variants. This is followed by selection on modifier genes, which shift hormonal titers or hormonal response (the JH titer in this study). This results in the evolution of either the threshold, or the population distribution about the threshold (*21*), in such a way that the population crosses the phenotypic threshold in response to temperature changes (Fig. 4). The genetic accommodation step results in both lowering of the threshold temperature and an increase in the steepness of the threshold, so the traits become more discrete.

The wild-type population is too far from the threshold, and no temperature fluctuation is sufficient to cross the threshold. Thus, we can think of the *black* mutation as a sensitizing mutation that brings the JH titer of the population closer to the threshold. Given the robustness of most traits to environmental perturbations, it is likely that many traits have thresholds that cannot be crossed without an initial sensitizing mutation that alters a homeostatic mechanism. After plasticity is exposed through the sensitizing mutation, selection can act to genetically accommodate the novel alternative phenotype.

Previous studies have shown that heat-shock proteins (e.g., *hsp90*) can act as capacitors for genetic variation (*22*, *23*). Our results show that mechanisms that control developmental hormones may also act as capacitors for genetic variation. Genes that maintain the titer of a developmental hormone far above its threshold of activity can mask mutations in genes that alter the secretion of, or response to, the hormone. Such genes can therefore allow the accumulation of silent mutations whose effects only become evident when normal regulation of the hormone is disrupted. Hormones have critical and widespread roles in the regulation of postembryonic development (*18*, *22*), and genetic variation in hormonal regulation likely plays an important role in the evolution of postembryonic developmental processes (*3*).

Our results suggest that the evolution of highly nonlinear reaction norms, such as polyphenisms, does not depend on the origin of novel favorable mutations that produce a threshold response (*3*). Rather, mutations in the mechanism that controls hormone titer can shift the phenotypic threshold and reveal previously covert genetic variation. Subsequent small-scale changes in hormone titer, or in the timing of hormone secretion, can reveal progressively more genetic variation upon which selection can act to cause a gradual heritable shift in the threshold. Thus, although the loss of condition-dependence can occur by a single mutation (*24*), drift (*25*), or selection (this study), the evolutionary origin of discontinuous reaction norms involves a complex interplay of sensitizing mutations, environmental fluctuations, and quantitative genetic variation.

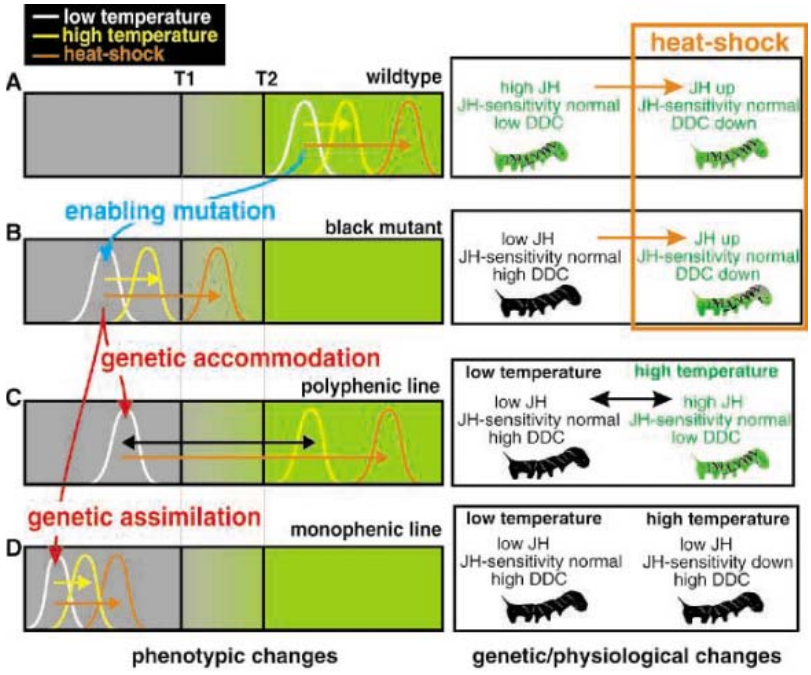

Fig. 4. (Left) Model for the evolution of a threshold trait at the phenotypic level. The evolutionary process required for the evolution of a threshold trait depends on the proximity of the population to the two thresholds (T1 and T2). Below T1, the phenotype is all black. Above T2, the phenotype is all green. Between T1 and T2, individuals express some intermediate phenotype. If the physiological control lies far from the phenotypic threshold (**A**), a mutation of larger effect or a sensitizing mutation is required to bring the population closer to the threshold (**B**). Once the population is closer to the threshold, the population can evolve a threshold response through genetic accommodation (**C**) or become canalized through genetic assimilation (**D**). (Right) The corresponding changes at the genetic/physiological level observed in this study. Unidirectional arrows indicate high-temperature–induced (yellow) and heat-shock–induced (orange) shifts. Bidirectional arrows indicate polyphenic shifts induced by temperature shifts.

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Resolving the Motional Modes That Code for RNA Adaptation

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Using a domain elongation strategy, we decoupled internal motions in RNA from overall rotational diffusion. This allowed us to site-specifically resolve a manifold of motional modes in two regulatory RNAs from HIV-1 with the use of nuclear magnetic resonance spin relaxation methods. Base and sugar librations vary on a picosecond time scale and occur within helical domains that move collectively at diffusion-limited nanosecond time scales. Pivot points are short, functionally important, and highly mobile internal loops. These spontaneous changes in RNA conformation correlate quantitatively with those that follow adaptive recognition of diverse targets. Thus, ligands may stabilize existing RNA conformations rather than inducing new ones.

Ribonucleic acids (RNAs) must adaptively change their conformation to meet the diverse requirements of their biological functions (*1*–*3*). The same RNA element can adopt conformations when assembling into a ribonucleoprotein complex that differ from those it adopts when carrying out its function (*4*, *5*). Similarly, ribozymes take on markedly different conformations during their catalytic cycles in order to meet the unique demands of substrate binding, catalysis, and product release (*6*, *7*).

The dynamic properties of RNA structures that are the basis of this plasticity remain poorly understood. This is largely due to difficulties in experimentally resolving complex superpositions of motional modes, each having unique amplitudes and time scales. These can include local librations at picosecond time scales, collective domain motions at nanosecond to millisecond time scales, and overall Brownian rotational diffusion at nanosecond to microsecond time scales (Fig. 1A). The individual contributions of these motional modes to spectroscopic observables cannot be readily resolved, especially when modes are physically coupled. For example, domain motions can change the RNA hydrodynamic shape and therefore the overall rotational diffusion. When these two motional modes have similar time scales, a dynamical coupling (*8*, *9*) develops that renders their spectroscopic contributions inseparable (Fig. 1A).

We describe a domain elongation strategy that allows us to resolve picosecond local motions and nanosecond domain motions by nuclear magnetic resonance (NMR) spectroscopy. We applied this strategy to two regulatory RNAs from HIV-1. The strategy involves extending the size of an RNA terminal domain through a stretch of Watson-Crick base pairs (Fig. 1B). This results in an elongated RNA (E-RNA) that has a hydrodynamic shape (and therefore a rotational diffusion profile) that is less sensitive to domain motions. Furthermore,

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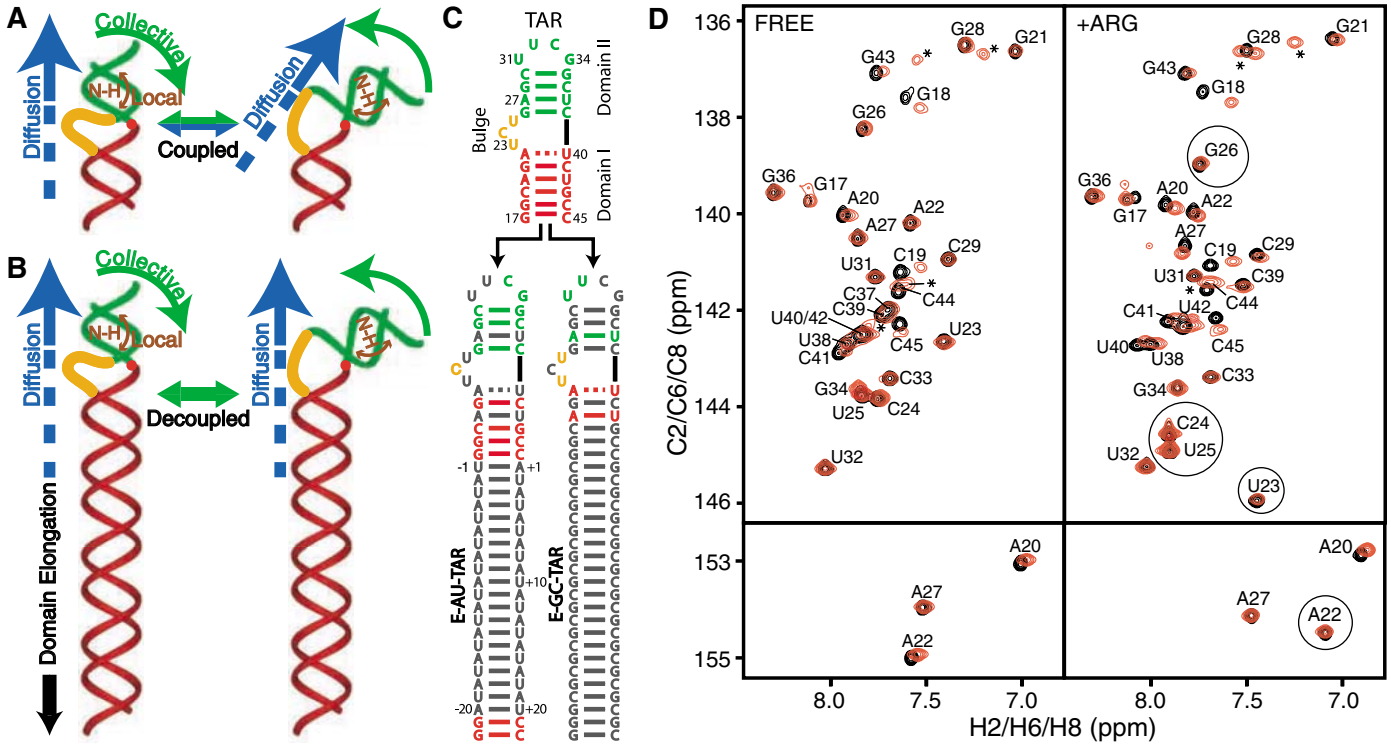

Fig. 1. Decoupling motional modes in RNA by domain elongation. (**A**) Collective motions lead to coupled changes in rotational diffusion described by the principal axis of the diffusion tensor, which is assumed parallel to the long axis of the RNA. (**B**) Decoupling collective motional modes by domain elongation. (**C**) NMR-invisible elongation of TAR RNA. The wild-type TAR loop is replaced by the more stable UUCG loop. Lines indicate Watson-Crick base pairs that are hydrogen-bonded, as detected by the J_{NN} correlation spectroscopy (COSY) experiment (*28*). Isotopically unlabeled residues are shown in gray. Two terminal G-C base pairs are added to domain I in E-TAR to maximize yields by in vitro transcription. (**D**) Two-dimensional (2D) ^{1}H-^{13}C heteronuclear single-quantum coherence (HSQC) spectra of the aromatic region of E-AU-TAR and E-GC-TAR (in red) overlaid on corresponding spectra of nonelongated TAR (in black) in free form (FREE) and bound to ARG (+ARG). Asterisks denote resonances that belong to two terminal guanine (G–21 and G–22) and cytosine (C+21 and C+22) residues in E-AU-TAR. Examples of bulge and neighboring residues that undergo ARG-induced chemical shift perturbations are highlighted in circles.

by slowing down overall tumbling, the elongation broadens the sensitivity of NMR relaxation, which is limited to internal motions occurring at time scales faster than overall tumbling (*10*). To avoid increasing NMR spectral overlap, we prepared two constructs in which stretches of either unlabeled A-U (E-AU-RNA) or unlabeled G-C (E-GC-RNA) base pairs were used for elongation in a background of uniformly $^{13}C/^{15}N$-labeled G-C or A-U nucleotides, respectively (Fig. 1C). The two constructs allowed acquisition of NMR data over the entire RNA target while keeping elongation residues "NMR-invisible."

We prepared (*11*) elongated constructs of the transactivation response element (TAR) from HIV-1 (*12*), a classic example of an RNA that can adaptively change its conformation and bind diverse targets (Fig. 1C) (*13*–*20*). The E-AU-TAR and E-GC-TAR chemical shifts were in excellent agreement with their nonelongated TAR counterpart, both in free form and when bound to argininamide (ARG) (a mimic of the TAR cognate protein target Tat) (Fig. 1D) (fig. S1) (*13*). This finding, together with degenerate ^{1}H chemical shifts observed for elongation residues (fig. S1), provided strong evidence that elongation residues adopt the expected helical structure without affecting TAR.

The spin relaxation properties of E-TAR exposed complex motional modes that were not detected in nonelongated TAR. Significant variations in resonance intensities—which, ignoring chemical exchange, report the net dynamics of a given site relative to the applied magnetic field—were observed in E-TAR. As expected, the lowest intensity indicative of overall tumbling of a well-structured helix was observed for the elongated domain I (Fig. 2A). Relative to this reference, many sites have higher intensities indicative of internal motions that are faster than overall tumbling (*11*). The high intensities of the bulge and neighboring residues provide evidence for a highly flexible domain-domain interface (Fig. 2A). The consistently higher intensities for base pairs in domain II relative to domain I suggest that domain II moves collectively across the flexible interface (Fig. 2A, inset). The even higher intensities for the UUCG loop indicate that it undergoes both collective and local motions (Fig. 2A). Most of these motional modes are not resolved in the intensities of nonelongated TAR (Fig. 2B). This can be attributed to couplings between domain motions and rotational diffusion as well as reduced sensitivity to internal motions due to faster overall tumbling.

We obtained further insight into the complex motional manifold by measuring resonance

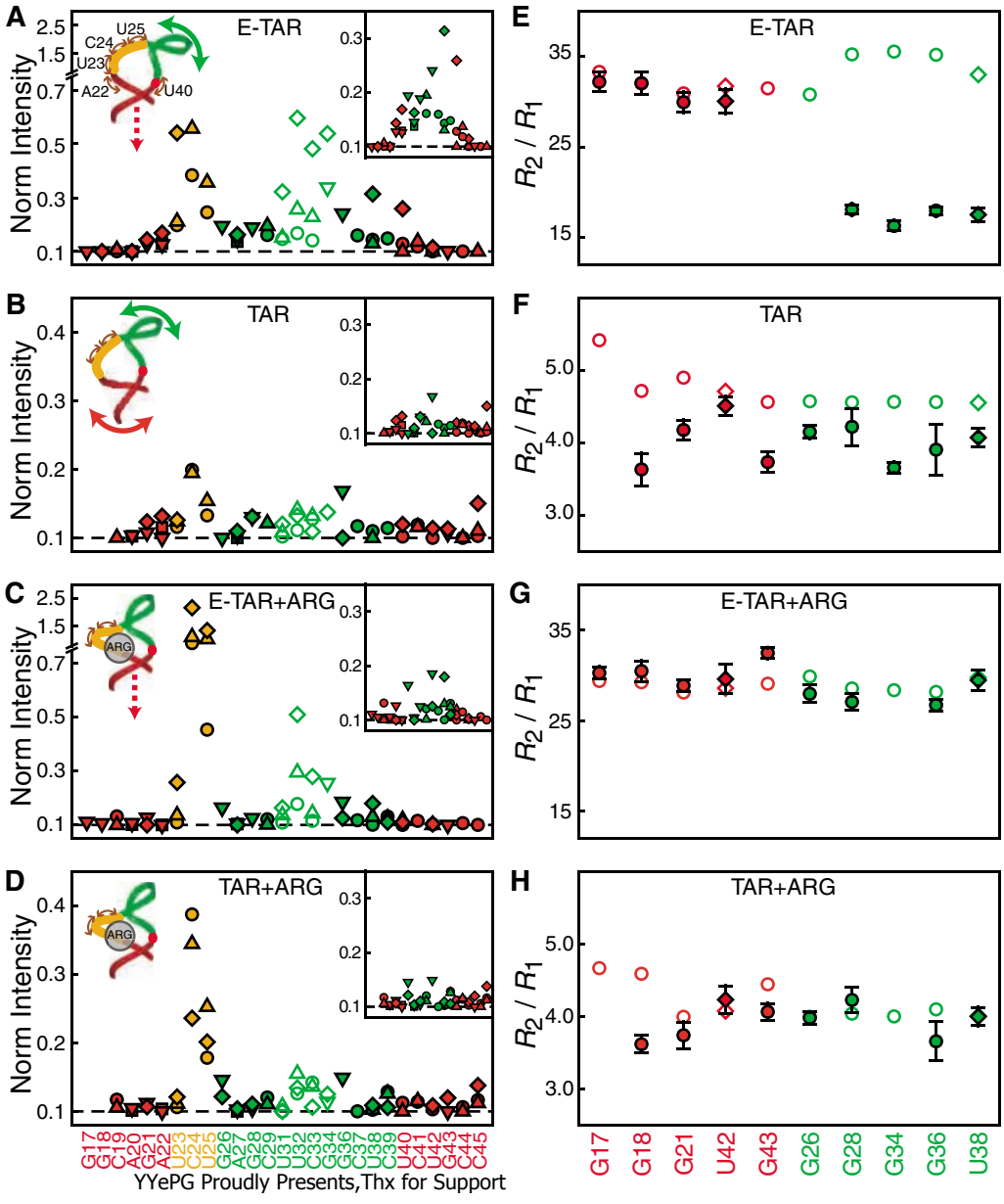

Fig. 2. RNA dynamics by motionally decoupled NMR. (**A** to **D**) Normalized resonance intensities (peak heights) measured from nonconstant-time 2D ^{1}H-^{13}C HSQC spectra. Shown are values for sugar C1′H1′ (diamonds) and base C2H2 (squares), C5H5 (circles), C6H6 (triangles), and C8H8 (inverted triangles) in (A) E-AU-TAR + E-GC-TAR, (B) TAR, (C) E-AU-TAR+ARG + E-GC-TAR+ARG, and (D) TAR+ARG. The intensity for each type of C-H spin is normalized to a minimum value of 0.1 independently for G-C and A-U residues. Insets show intensities for Watson-Crick residues only. The UUCG loop intensities are denoted by open symbols. (**E** to **H**) Ratios (R_2/R_1) of imino ^{15}N transverse (R_2) to longitudinal (R_1) relaxation rates measured for guanine (circles) and uridine (diamonds) residues in (E) E-AU-TAR + E-GC-TAR, (F) TAR, (G) E-AU-TAR+ARG + E-GC-TAR+ARG, and (H) TAR+ARG. Hydrodynamically predicted R_2/R_1 values are denoted by open symbols.

intensities in the E-TAR+ARG complex. Previous studies have shown that ARG stabilizes a coaxially aligned TAR conformation by interacting with residues at the interdomain interface (*13*, *14*, *21*). Consistent with an arrest of domain motions, ARG binding leads to a reduction in the relative intensity of most sites in domain II, including residues (e.g., UUCG loop) far removed from the ARG binding pocket (Fig. 2C). This is accompanied by a reduction in the mobilities of residues at the domain-domain interface (U23, A22, and U40) that are known to interact with one another or ARG upon complex formation (Fig. 2C) (*13*, *14*, *21*). The ARG arrest of domain motions exposes the local mobility of the UUCG loop as intensities (Fig. 2C) that correlate well (R = 0.99) with its local motional amplitudes derived independently from a previous NMR relaxation study (*22*). Although ARG binding induces similar intensity changes in TAR, these are significantly less pronounced and the arrest of domain motions goes completely undetected (Fig. 2D).

Independent support for domain motions in E-TAR was obtained by measuring imino ^{15}N relaxation data (*23*) for guanine and uridine residues (*11*) (fig. S2 and table S1). The uniformly smaller ratios of transverse (R_2) to longitudinal (R_1) relaxation rates (R_2/R_1) observed for every site in domain II as compared to domain I in E-TAR confirmed the existence of domain motions that reorient every site in domain II relative to domain I (Fig. 2E) (fig. S3). In contrast, the similar R_2/R_1 values observed for the two hydrodynamically equivalent domains in TAR confirmed that in the absence of elongation, domain motions cannot be separated from rotational diffusion (Fig. 2F). Consistent with an arrest of domain motions, ARG binding leads to an increase in the domain II R_2/R_1 values in E-TAR such that they approach the values measured in domain I (Fig. 2G). In contrast, this dynamical arrest goes undetected in nonelongated TAR (Fig. 2H). The agreement between the measured E-TAR R_2/R_1 values and hydrodynamic calculations (*24*) using an extended A-form helix for domain I provides further support that elongation residues adopt the expected helical structure (Fig. 2, E and G).

Model-free analysis (*10*, *25*, *26*) of the E-TAR ^{15}N relaxation data (*11*) allowed us to quantitatively resolve overall rotational diffusion, local N-H fluctuations, and domain motions (Fig. 3A) (table S2). The observed time constant for E-TAR molecular rotational diffusion (τ_m = 18.9 ns) is in excellent agreement with hydrodynamic predictions (τ_{calc} = 19.5 ns). Local N-H fluctuations have effective time constants that are on the order of picoseconds (τ_e = 24 to 33 ps). These fast motions have amplitudes spanning S_f^2 = 0.79 to 0.89 (S_f^2 varies between 0 and 1 for maximum and minimum motions). The shorter domain II displays slightly larger amplitudes on average, with the largest amplitudes observed for U38, which is consistent with its high resonance intensities (Fig. 2A, inset). This motion is likely important in the formation of a U38-A27·U23 base-triple that accompanies adaptive recognition (*13*, *21*). The N-H sites in domain II also experience slower and larger amplitude (S_s^2 = 0.68 to 0.76) domain motions whose time constants (τ_s = 1.5 to 1.9 ns) approach the hydrodynamically predicted time constant for rotational diffusion of domain II alone (τ_m = 2.2 ns). Thus, the two domains reorient independently of one another at their own diffusion-limited time scales across a highly unstructured interface. These domain motions occur at time scales approaching that of TAR overall rotational diffusion ($\tau_m \sim 6$ ns), making separation of the two modes difficult in the absence of elongation. ARG binding arrests the domain motions in E-TAR and leads to a uniform reduction in the librational amplitudes (S_f^2 = 0.86 to 0.95) (Fig. 3B). The time constant for E-TAR+ARG rotational diffusion (τ_m = 18.4 ns) is also in excellent agreement with hydrodynamic predictions (τ_{calc} = 18.2 ns).

The subnanosecond motional modes observed in E-TAR involve small kinetic barriers and therefore constitute fundamental dynamics of the RNA main chain. We confirmed the generality of these motional modes by applying elongated NMR spectroscopy (*11*) to characterize the dynamics of a different RNA, SL1$_m$ (*27*), also derived from HIV-1 (Fig. 3C). Unlike TAR, the two helical domains in SL1$_m$ are linked by a purine-rich internal loop that is juxtaposed by different Watson-Crick base pairs (Fig. 3C). Despite this different linker, the resonance intensities (figs. S4 and S5) and ^{15}N relaxation data (figs. S6 and S7 and table S1) measured in E-SL1$_m$ revealed domain motions that once again evade detection in nonelongated SL1$_m$. Model-free analysis (*10*, *25*, *26*) of the E-SL1$_m$ ^{15}N relaxation data yielded local librations and collective domain motions similar to those observed in E-TAR (Fig. 3C) (table S2).

Such fundamental motional modes could provide a molecular basis for RNA structural adaptation. TAR is one of the best documented examples of an RNA molecule that can adopt different conformations and thereby bind to diverse targets. The current repertoire of such "adapted" HIV-1 TAR conformations includes eight high-resolution NMR and x-ray structures

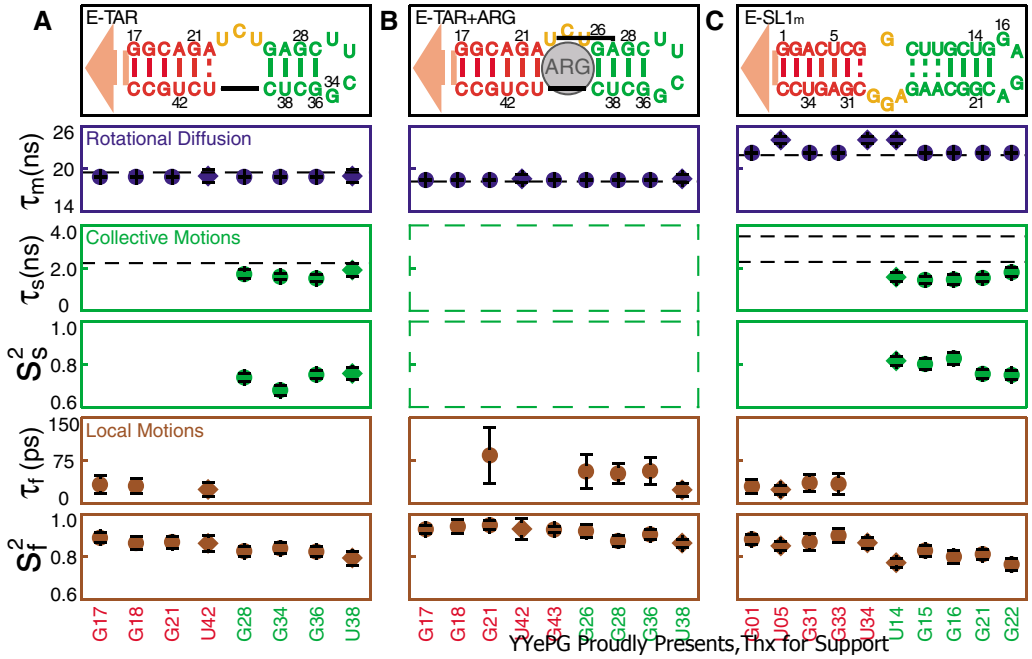

Fig. 3. Resolving nanosecond and picosecond motional modes in RNA. Vertical lines in the RNA secondary structures indicate hydrogen-bonded Watson-Crick base pairs as detected by the J_{NN} COSY experiment (*28*). Shown are time constants (τ) and amplitudes (S^2) for rotational diffusion (blue), collective (green), and local (brown) motions in (**A**) E-AU-TAR + E-GC-TAR, (**B**) E-AU-TAR+ARG + E-GC-TAR+ARG, and (**C**) E-AU-SL1$_m$ + E-GC-SL1$_m$. Black horizontal dashed lines correspond to the hydrodynamically computed time constant for overall rotational diffusion of E-RNA and domain II alone. For E-SL1$_m$, a range of domain II time constants is shown to indicate inclusion and exclusion of base pairs (C9-G26, U10-A25, and U11-A24) that do not have detectable hydrogen bonds.

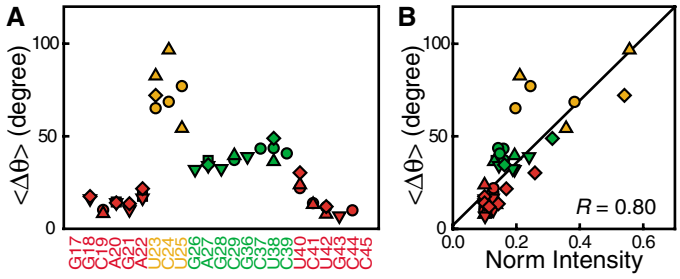

Fig. 4. Site-specific comparison of RNA dynamics and structural adaptation. **(A)** Mean angular difference $\langle \Delta\theta \rangle$ in the orientation of sugar and base C-H bond vectors across eight different HIV-1 TAR structures (in free form and bound to seven distinct targets) after superposition of residues in domain I. The symbols denote different C-H bonds as described in Fig. 2. The UUCG loop is excluded because it is absent from the TAR structures examined. **(B)** Correlation plot between $\langle \Delta\theta \rangle$ and the corresponding free E-TAR intensities (shown in Fig. 2A). The line corresponds to a linear best fit.

of TAR in the absence of ligands (*15*) and bound to Tat-derived peptides (*14*), divalent ions (*16*), and five chemically distinct small molecules (*17*–*20*). These TAR structures differ significantly (structures superimpose with an all-atom root mean square deviation of 4.7 Å) both in the global orientation of helical domains (interhelical angle spanning ~5° to ~47°) and in the local structure of the binding pocket, which comprises the bulge and neighboring residues (fig. S8).

To assess the relationship between adaptive structural changes and internal motions, we quantified the magnitude of TAR structural adaptation by computing the mean angular variation $\langle \Delta\theta \rangle$ in the orientation of C-H bonds across the eight structures, using domain I as a reference for superimposing structures (*11*). We then compared these adaptive structural changes with the free E-TAR intensities (Fig. 2A), which provided a corresponding domain I–referenced measure of internal motions. Remarkably, the magnitude of adaptive structural change observed at a given site (Fig. 4A) was quantitatively correlated (R = 0.80) to the degree of spontaneous internal motions at the site in the free RNA (Fig. 4B). Thus, a hierarchical network of local and collective internal motional modes occurring at nanosecond and faster time scales underlies RNA's ability to adaptively change conformation.

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Structure of Human Urokinase Plasminogen Activator in Complex with Its Receptor

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The urokinase plasminogen activator binds to its cellular receptor with high affinity and initiates signaling cascades that are implicated in pathological processes including tumor growth, metastasis, and inflammation. We report the crystal structure at 1.9 angstroms of the urokinase receptor complexed with the urokinase amino-terminal fragment and an antibody against the receptor. The three domains of urokinase receptor form a concave shape with a central cone-shaped cavity where the urokinase fragment inserts. The structure provides insight into the flexibility of the urokinase receptor that enables its interaction with a wide variety of ligands and a basis for the design of urokinase-urokinase receptor antagonists.

Urokinase plasminogen activator (uPA) together with its cell surface receptor (uPAR) mediate a variety of biological activities at the cell surface, including plasminogen activation (*1*), extracellular matrix remodeling (*2*, *3*), growth-factor activation (*4*), and the initiation of intracellular signaling (*5*, *6*). The uPA system plays an important role in cell adhesion, migration, invasion, and tissue remodeling (*5*, *7*–*9*). The importance of the uPA-uPAR system in tumor biology and metastasis has been well established. Elevated levels of soluble uPAR (suPAR) in cancer cells (*10*) usually indicate a poor prognosis for patient survival (*11*). Inhibition of uPAR expression has been shown to inhibit tumor cell invasiveness (*12*), prevent metastasis (*13*), reverse invasive tumor behavior (*14*), and increase the duration of tumor latency (*15*). These findings suggest that uPAR antagonists may be useful therapeutically as inhibitors for tumor progression.

uPA is composed of a carboxyl-terminal serine protease domain and a modular amino-terminal fragment (ATF) that contains all of the determinants required for binding to its receptor. The ATF forms a stable complex with uPAR, with a K_d of 0.28 nM (*16*). uPAR, a glycoprotein, contains 283 amino acid residues linked to the cell surface through a carboxyl-terminal glycosylphosphatidylinositol (GPI) anchor (*16*). The suPAR variant without the GPI anchor has been identified in pathological conditions (*10*); it binds to uPA at an affinity indistinguishable from the GPI-anchored full-length

uPAR (*16*), which indicates that suPAR is an appropriate candidate for the structural study of the uPA-receptor complex.

The crystals of the suPAR-ATF-ATN615 complex were formed by the microdialysis method; ATN615 is the Fab fragment of an antibody against suPAR. The structure was refined to 1.9 Å with R_{cryst} and R_{free} values of 0.237 and 0.274, respectively (table S1). The electron density map shows that the majority of the structures of suPAR and the ATF were well ordered in the complex (fig. S1). Some regions (residues 35 to 37, 81 to 91, 130 to 139, and 249 to 251 of suPAR and 133 to 145 of ATF) and the terminal residues (1 to 10) of ATF were omitted in the structure owing to the lack of adequate electron density. The three proteins in the ternary complex are arranged in a linear elongated complex that is 141 Å in length (Fig. 1A). The D1 and D2 domains of suPAR bind to ATF, whereas the D3 domain is the recognition site of the antibody ATN615.

Our structure reveals both domains of the ATF: the growth factor–like domain (GFD, residues 10 to 43) and the kringle domain (residues 50 to 132) (Fig. 1B). The salient features in the GFD domain are two short β strands (residues 18 to 22 and 30 to 32) connected by an Ω-loop (residues 23 to 29), a major receptor-binding determinant (*9*). One of the disulfide bonds between residues 11 and 19 was absent in our structure, possibly as a result of the disorder of the first 10 residues of the ATF. The kringle domain contains a two-stranded β sheet, two short α helices, and three disulfide bonds.

Previous solution structures of unbound ATF determined by nuclear magnetic resonance (NMR) suggested that the GFD and kringle domains of the ATF exhibit a high degree of structural independence involving little or no interdomain interaction (*17*). However, in the ternary complex, the ATF is constrained, with the two adjacent domains packed tightly and forming hydrophobic interaction with each other (Fig. 1B).

The structure of suPAR, consisting of 17 antiparallel β strands with three short α helices, is organized into three domains (D1, D2, and D3) (Fig. 2A). The D1 domain is composed of a six-stranded continuous antiparallel β sheet containing three disulfide bonds. The β5 strand of uPAR is highly conserved across different species and is an essential strand for D1-D2 domain association (Fig. 2B). The D2 domain forms a β sheet with six strands, a short α helix between β7 and β8, and four disulfide bonds. The β10 strand of the D2 domain twists more than 45° at Gly^{146} so that the amino-terminal half (residues 143 to 145) is parallel with β9 of the D2 domain, whereas the carboxyl-terminal half (residues 147 to 149) lines up with the β5 of the D1 domain; these alignments suggest its role in joining two domains (Fig. 2B). Also involved in D1-D2 association are β7, β8, β10,

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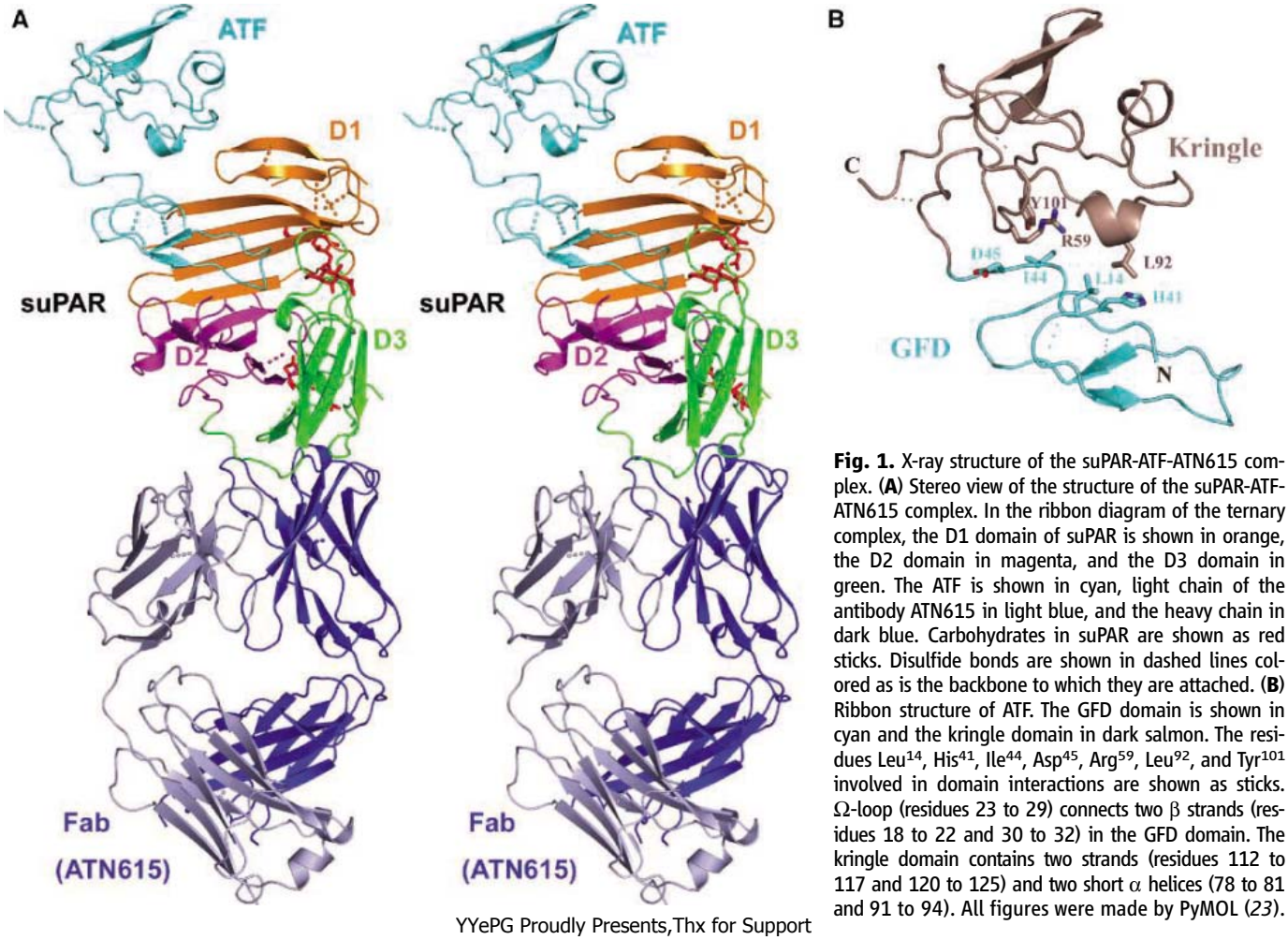

Fig. 1. X-ray structure of the suPAR-ATF-ATN615 complex. (**A**) Stereo view of the structure of the suPAR-ATF-ATN615 complex. In the ribbon diagram of the ternary complex, the D1 domain of suPAR is shown in orange, the D2 domain in magenta, and the D3 domain in green. The ATF is shown in cyan, light chain of the antibody ATN615 in light blue, and the heavy chain in dark blue. Carbohydrates in suPAR are shown as red sticks. Disulfide bonds are shown in dashed lines colored as is the backbone to which they are attached. (**B**) Ribbon structure of ATF. The GFD domain is shown in cyan and the kringle domain in dark salmon. The residues Leu^{14}, His^{41}, Ile^{44}, Asp^{45}, Arg^{59}, Leu^{92}, and Tyr^{101} involved in domain interactions are shown as sticks. Ω-loop (residues 23 to 29) connects two β strands (residues 18 to 22 and 30 to 32) in the GFD domain. The kringle domain contains two strands (residues 112 to 117 and 120 to 125) and two short α helices (78 to 81 and 91 to 94). All figures were made by PyMOL (*23*).

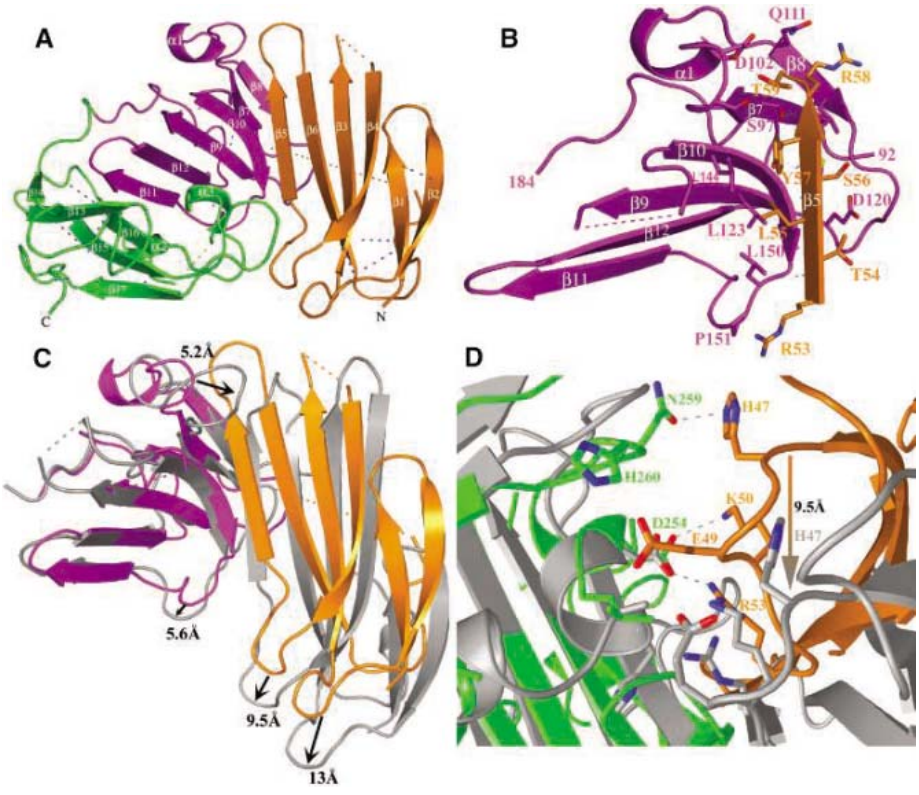

Fig. 2. (**A**) Domain structure of suPAR in the suPAR-ATF complex. The D1 domain (orange, residues 1 to 80) contains six β strands (β1, residues 2 to 7; β2, 10 to 16; β3, 23 to 32; β4, 38 to 46; β5, 53 to 58; β6, 63 to 71). The D2 domain (magenta, residues 93 to 191) contains six β strands (β7, 94 to 99; β8, 111 to 114; β9, 121 to 128; β10, 143 to 149; β11, 156 to 161; β12, 164 to 171) and a short α helix (α1, 104 to 107). The D3 domain (green, residues 192 to 283) contains five β strands (β13, 193 to 198; β14, 211 to 214; β15, 220 to 226; β16, 237 to 242; β17, 262 to 266) and two short α helices (α2, 244 to 246 and α3, 253 to 256). Disulfide bonds are shown in dashed lines (blue). The disordered loops are connected by the dash line colored as is the backbone to which they belong. (**B**) Interaction of the D1 and D2 domain. The β5 strand in the D1 domain is critical for association between the D1 and D2 domains. Residues involved in the D1-D2 interaction are shown as sticks. (**C**) D1-D2 domains of suPAR from this study (orange and magenta) were superimposed with suPAR bound with an antagonist peptide (gray) (PDB code 1YWH). The two structures were aligned using the Cα atoms from the D2-D3 domains. The D1 domain shows 20.5° rotation and 9.5 Å displacement between the two structures. (**D**). Variation in the D1-D3 domain interface between ATF-bound suPAR (orange for D1 and green for D3) and peptide-bound suPAR (gray) (PDB code 1YWH). The residues His^{47}, Glu^{49}, Lys^{50}, Arg^{53}, Leu^{252}, Asp^{254}, Asn^{259}, and His^{260} (shown as sticks) are key residues maintaining the D1D3 domain interface in suPAR-ATF structure.

and a loop (100 to 104), resulting in six hydrogen bonds, a hydrophobic cluster on one side of β5, several charge interactions on the other side of the β5, and an interface of 1188 Å^2 (Fig. 2B). The β11 and β12 of the D2 domain are major determinants for the D2-D3 association and form a larger interface (1576 Å^2) with the D3 domain. The D3 domain consists of a bundle of five β strands, with two short α helices connecting the β16 and β17. Half of β13, a part of β15, β16, α2, α3, and a loop (residues 215 to 219) of the D3 domain are involved in D2-D3 association. The D1 and D3 domains also make contact with each other. The loop (226 to 237) and the α3 of the D3 domain are involved in binding with the loop (47 to 53) of the D1 domain, resulting in three hydrogen bonds between two domains [His^{47}-Asn^{259}, Lys^{50}-Asp^{254}, and Arg^{53}-Asp^{254} (Fig. 2D)] and an interface of 476 Å^2.

Superposition of the current suPAR structure with suPAR in complex with a small peptidyl inhibitor determined at 2.7 Å resolution (*18*) shows some important differences. Comparison between the individual domains of suPAR indicates only minimal differences (see the SOM Text). However, dramatic differences were observed in the relative orientation of these domains (Fig. 2, C and D). When the D2-D3 domains between the two suPAR structures were superimposed, their D1 domains showed a rotation of 20.5° with a root-mean-square deviation of 9.5 Å (Fig. 2C). Compared with our suPAR structure, the three loops (residues 16 to 23, 46 to 52, and 149 to 156) in the suPAR-inhibitor structure move away from the center of the binding cavity by about 13, 9.5, and 5.6 Å, respectively (Fig. 2C), and six β strands in the D1 domain move about 5 to 10 Å in order to enlarge the bottom of the binding cavity to accommodate the peptidyl inhibitor. Two loops (residues 99 to 104 and 128 to 143) located at the opening of the suPAR cavity are also significantly different between the two structures. Compared with the suPAR-peptide structure, loop 99 to 104 in the D2 domain of suPAR-ATF moves 5.2 Å away from the D1 domain (Fig. 2C) in order for suPAR to accommodate ATF binding. The domain associations also differ significantly between the two suPAR structures. For example, the D1-D3 interface in the suPAR-peptide complex is 169 Å^2 compared with 476 Å^2 in the suPAR-ATF complex. In addition, no hydrogen bonds were observed in this interface in the suPAR-peptide complex. These results indicate that the binding pocket of uPAR is greatly influenced by the nature of the ligands, with different ligands accommodated by flexibility in the domain-domain association and in the position of loops connecting β strands.

The three domains of suPAR form a concave shape with a diameter of about 52 Å and a height of 27 Å (Fig. 3A). At the center is a cone-shaped cavity with a wide opening (25 Å) that is 14 Å deep and contains a large accessible surface for ATF binding. The ATF inserts into the cavity of uPAR, but does not occupy the whole cavity (Fig. 3, B and C). The complementary surface at this interface is quite large, with a total surface area of 1171 Å^2.

The suPAR-ATF interface can be divided into three contact regions. The first region is formed mainly by one stretch of residues in the GFD domain of uPA (Ser^{21}, Asn^{22}, Lys^{23}, and Tyr^{24}) and contacts mainly the D2 domain of suPAR (with the exception of Ser^{26} of the GFD domain that interacts with the Arg^{25} in the D1 domain of suPAR) (Fig. 3, B and C). This region is buried deep in the suPAR cavity and has both hydrogen bonds and polar interactions between uPA and its receptor. Five of six hydrogen bonds in the suPAR-ATF interface (table S2) are in this region. Tyr^{24} of the ATF forms hydrogen bonds with Arg^{53} of the D1 domain and His^{166} of the D2 domain of suPAR, and a polar interaction with Asp^{254} of the D3 domain (Fig. 3C). This is consistent with biochemical studies (*19*, *20*) suggesting that residue Tyr^{24} is an important receptor-binding determinant. The second region of the suPAR-ATF interface is located in the hydrophobic patch at the inner surface near the opening of the suPAR cavity and is formed mainly by the residues in the D1 domain β strands β3 (Leu^{31} and Val^{29}), β4 (Leu^{40}), β5 (Leu^{55}), and β6 (Leu^{66}) (Figs. 2A and 3C). This patch interacts with the ATF hydrophobic

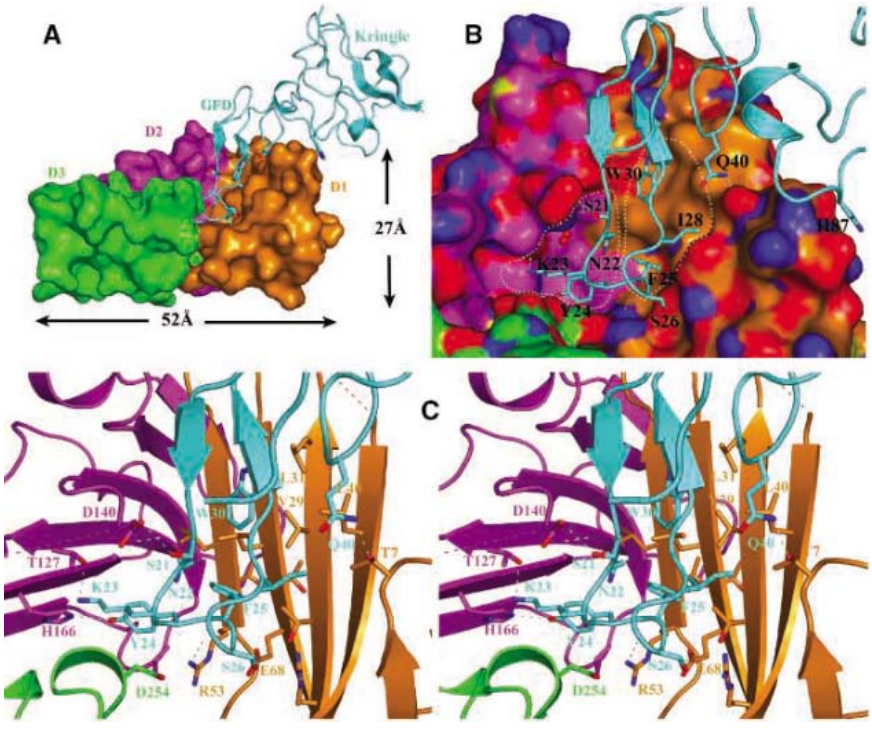

Fig. 3. The suPAR-ATF binding surface. The carbon atoms of the D1 domain of uPAR are shown in orange, the D2 in magenta, and the D3 in orange. The ATF is shown in a ribbon diagram in cyan. (**A**) Molecular surface representation of the overall suPAR-ATF binding. The three uPAR domains form a conical cavity with a wide opening (25 Å) and large depth (14 Å) that are involved in the ATF binding. (**B**) Surface representation of the uPAR-ATF binding. The circled areas are regions 1 and 2 (from left to right) of uPAR-ATF interface. Oxygen atoms are shown in red, nitrogen atoms in blue, and sulfur in yellow. Waters involved in uPAR-ATF binding are shown as red spheres. Hydrogen bonds are shown as dashed lines (light blue). (**C**) Detailed interaction of suPAR (ribbon representation) and the ATF in stereoview. Thr^{8}, Arg^{53}, Glu^{68}, Thr^{127}, and His^{166} of suPAR form hydrogen bonds with Ser^{21}, Lys^{23}, Tyr^{24}, Ser^{26}, and Gln^{40} of ATF.

residues, Phe^{25}, Ile^{28}, and Trp^{30} (Fig. 3, B and C; fig. S1). This region forms significant hydrophobic interactions and is also a major contributor to the high-affinity uPAR-uPA binding. The third region is located at the edge of the cavity and consists of a hydrogen bond and van der Waals contacts between the D1 domain of suPAR and the residues of ATF, including the kringle domain (Fig. 3A). The current structure not only confirms that the D1 and D2 domains of uPAR play a critical role in the binding of uPA, but also points out the role of the D3 domain in the uPA-uPAR interaction. Helix α3 of the D3 domain contacts the ATF through van der Waals interactions, forms a wall of the suPAR cavity, and closes up the cavity by interacting with the D1 domain (Fig. 2D). Taken together, all three uPAR domains and both uPA domains are necessary for high-affinity uPA-uPAR interaction.

Substantial species-specificity exists in the uPA-uPAR interaction with little or no binding observed between the human and mouse proteins (*21*). This is important as mouse cancer models are frequently used to assess the value of interventions targeting uPAR for treatment of human diseases. Sequence alignment of the uPAR residues involved in uPA binding shows that most of the hydrophobic residues (four out of five; Val^{29}, Leu^{40}, Leu^{55}, and Leu^{66}) and the charged residues (five out of six; Thr^{8}, Arg^{53}, Glu^{68}, Thr^{127}, Asp^{140}, and His^{166}) are conserved in all different species of uPAR studied to date. The only significant amino acid difference is Glu^{31} in mouse compared with Leu^{31} in human uPAR. The current structure shows that the Leu^{31} is part of a hydrophobic patch (Fig. 3C, region 2) and interacts with hydrophobic residues of ATF. This difference may explain the weak interaction of mouse uPAR with human uPA. The sequence alignment of the receptor binding residues of uPA in different species (table S3) indicates the replacement of Trp^{30} in human uPA with an Arg^{30} in mouse uPA. Trp^{30} is involved in hydrophobic interactions with the human suPAR hydrophobic patch (Fig. 3C, region 2), thus Arg^{30} may prevent mouse uPA from binding to human uPAR. "Humanization" of the mouse GFD domain through substitution of Trp at Arg^{30} (Arg30Trp mutation) along with other mutations (Tyr22Asn) restored high-affinity binding for human uPAR (*22*), consistent with this interpretation.

This structure of the uPAR-ATF complex provides a structural model to unify and to validate the large body of biochemical studies that have been published describing the uPAR-uPA interaction (*3*, *9*). The high-resolution structure of this protein-protein complex will also provide a platform for rational design of inhibitors to interfere with the uPAR-uPA interaction and its pathophysiological consequences.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5761/656/DC1
Materials and Methods
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Fig. S1
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References and Notes

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Fish Population and Behavior Revealed by Instantaneous Continental Shelf–Scale Imaging

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Until now, continental shelf environments have been monitored with highly localized line-transect methods from slow-moving research vessels. These methods significantly undersample fish populations in time and space, leaving an incomplete and ambiguous record of abundance and behavior. We show that fish populations in continental shelf environments can be instantaneously imaged over thousands of square kilometers and continuously monitored by a remote sensing technique in which the ocean acts as an acoustic waveguide. The technique has revealed the instantaneous horizontal structural characteristics and volatile short-term behavior of very large fish shoals, containing tens of millions of fish and stretching for many kilometers.

There is substantial evidence that fish populations are rapidly declining worldwide (*1*, *2*), yet with conventional sea-going survey methods (*3*–*7*) it is difficult to accurately enumerate fish populations (*6*, *8*, *9*) and nearly impossible to study the behavioral dynamics of very large social groups or shoals of fish (*10*), including the impacts of population decline (*11*, *12*). This is because conventional methods rely on highly localized measurements made from slow-moving research vessels, which typically survey along widely spaced line transects to cover the vast areas that fish inhabit, and so greatly undersample the environment in time and space, leaving highly ambiguous records. We assessed fish populations with a remote sensing technology involving ocean acoustic waveguide propagation that surveys at an areal rate that is roughly one million times greater than that of conventional fish-finding methods. The waveguide technology makes it possible to continuously monitor fish population dynamics, behavior, and abundance, with minute-to-minute updates over thousands of square kilometers, producing records without aliasing (*13*, *14*) in time and space.

With the waveguide remote-sensing technology, we observed (i) instantaneous hori-

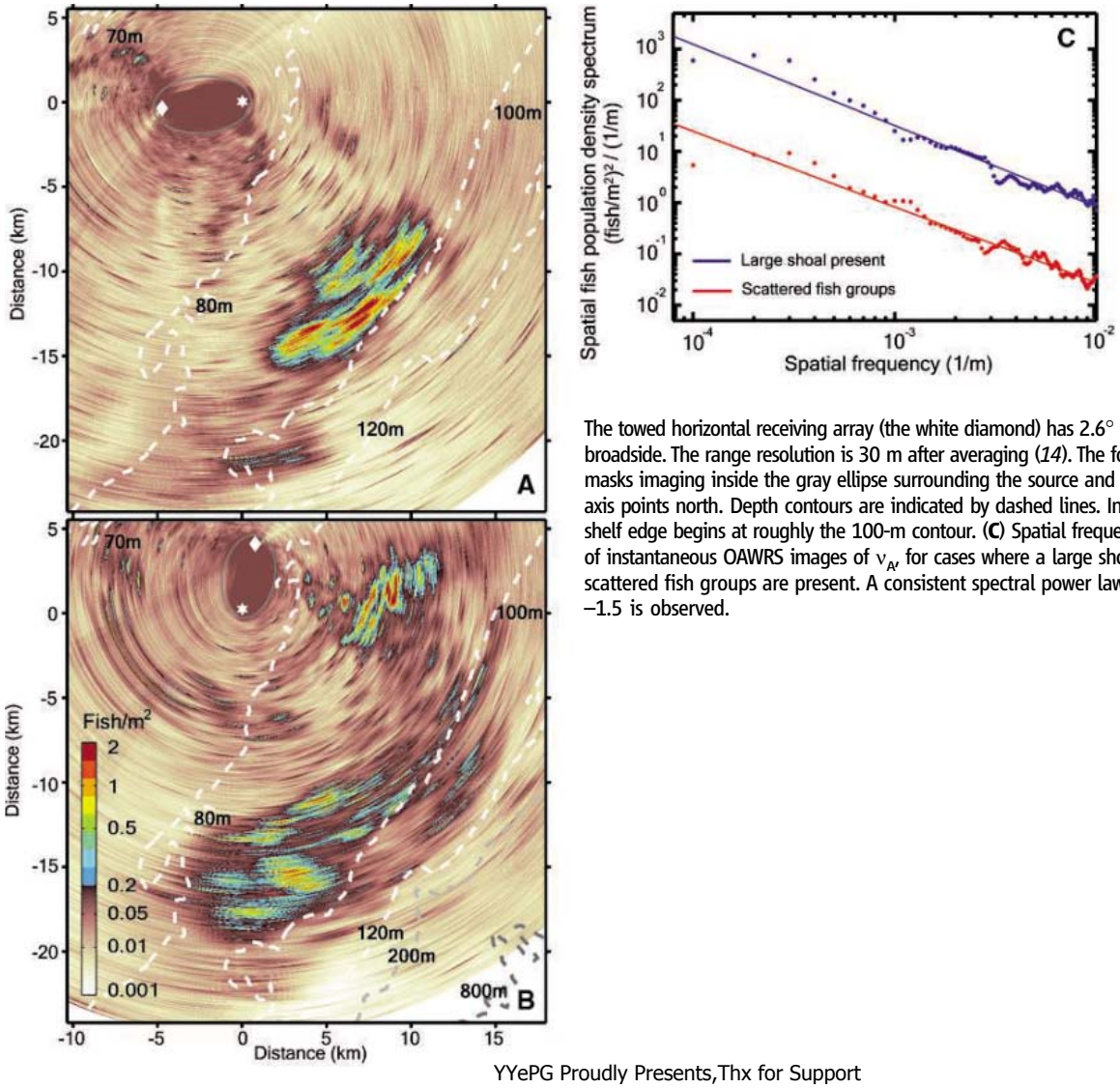

Fig. 1. Two instantaneous areal density images of fish shoals near the continental shelf edge obtained by ocean acoustic waveguide remote sensing (OAWRS) at (**A**) 09:32 EDT, 14 May 2003, and (**B**) 08:38 EDT, 15 May 2003, each acquired within 40 s. ν_A is shown in color. The moored source (the white star) is the coordinate origin in all figures at 39.0563°N, 73.0365°W. The towed horizontal receiving array (the white diamond) has 2.6° azimuthal resolution at array broadside. The range resolution is 30 m after averaging (*14*). The forward propagation of sound masks imaging inside the gray ellipse surrounding the source and receiver. The positive vertical axis points north. Depth contours are indicated by dashed lines. In (A) and (B), the continental shelf edge begins at roughly the 100-m contour. (**C**) Spatial frequency spectra, based on scores of instantaneous OAWRS images of ν_A, for cases where a large shoal is present and only small scattered fish groups are present. A consistent spectral power law of spatial frequency to the –1.5 is observed.

zontal structural characteristics, (ii) temporal evolution, and (iii) the propagation of information in very large fish shoals, containing tens of millions of fish and extending for many kilometers. All of these observations were made from distances that were typically greater than 10 km from the shoal boundaries and with sound that was at least three orders of magnitude less intense than conventional fish-finding sonar. This is possible because underwater acoustic remote sensing in the ocean (*14*–*19*) relies on the capacity of the continental shelf environment to behave as an acoustic waveguide, in which sound propagates over long ranges via trapped modes that suffer only cylindrical spreading loss rather than the spherical loss suffered in conventional fish-finding sonar technologies (*7*). The conventional approach employs only waterborne propagation paths that are restricted to much shorter ranges, on the order of the local water depth, and much higher frequencies, where attenuation is much greater (*14*).

Typical realizations of the instantaneous horizontal structure of very large fish shoals, comprising perhaps the largest massing of animals ever instantaneously imaged in nature, are shown in Fig. 1, A and B. The images are from data acquired during our May 2003 experiment (*14*) near the edge of the continental shelf 200 km south of Long Island, New York, USA. We found population centers of various size, interconnected by a network of "fish bridges" at various scales. These made the shoal shown in Fig. 1A a contiguous entity that stretched for over 10 km. A similar situation is seen in the very large southern and smaller northern shoal of Fig. 1B. All shoals exhibit large internal vacuoles and hourglass patterns previously observed only in fish groups that were many orders of magnitude smaller in area (*9*, *10*). The shoals are often very sharply bounded on the seaward side by a specific bathymetric contour of the continental shelf edge, as in Fig. 1A. This geophysical boundary apparently organizes the shoal horizontally as a social entity and may also be a navigational landmark for distant migrations (*20*, *21*). Although we found all large shoals between roughly the 80- to 100-m bathymetric contour, fish assemblages changed dramatically over time in any given region, as shown in Fig. 1 from one morning (Fig. 1A) to the next (Fig. 1B). The overall background population, for example, increases significantly from Fig. 1A to 1B, with a dense distribution of very small groups of fish appearing between the very large southern shoal and the smaller northern one. Under some circumstances, these may provide the building blocks for the fish bridges that bind a shoal together. Annual trawl surveys conducted earlier in the season and historically (*14*, *22*), as well as our visual and behavioral observations at sea, indicate that Atlantic herring, scup, hake, and black sea bass are likely species candidates in the large shoals.

The instantaneous horizontal spatial distribution of fish over wide areas follows a fractal or power-law spectral process, as quantitatively shown in Fig. 1C. Instantaneous structural similarity then exists at all scales observed, from tens of meters to tens of kilometers, and suggests that similar underlying behavioral mechanisms may be responsible for structures at all scales. This supports the qualitative argument for a fractal process in (*9*) but not the disjoint clustering of population centers that is perhaps implied there. The power law is invariant to the size of the largest fish group present, and so remains constant if an area contains a very large shoal or only much smaller scattered groups of fish, as shown in Fig. 1C. Our observations that very large shoals are structurally similar to much smaller fish groups must be a consequence of the power law. Knowledge of this power law now enables more accurate statistical predictions of the instantaneous spatial distribution of fish populations over wide areas.

Simultaneous measurements from both the conventional and the waveguide remote-sensing systems show excellent agreement in fish population density at identical time-space points along the conventional line transect (light blue line in Fig. 2, A to D), but only the waveguide technology senses two-dimensional (2D) horizontal structure and temporal change. Both systems reveal dense populations of fish at time-space points α, β, and γ, and neither system registers fish at δ beyond the shoal's seaward edge. The sharp and extensive 2D horizontal boundary of the shoal seen with the waveguide technology along the shelf edge in Figs. 1A and 2, A to D, is too transitory to be inferred from or practically measured with conventional line-transect methods, even from a series of transects. Nor can the conventional system detect or recognize the network of interconnecting bridges between population centers that waveguide technology has shown to be part of the fundamental structure of shoals. For example, the large but transitory bridge connecting the northern and southern wings of the shoal in Fig. 2, A to D, gives it a classic hourglass pattern, never previously observed over such a large scale. This is

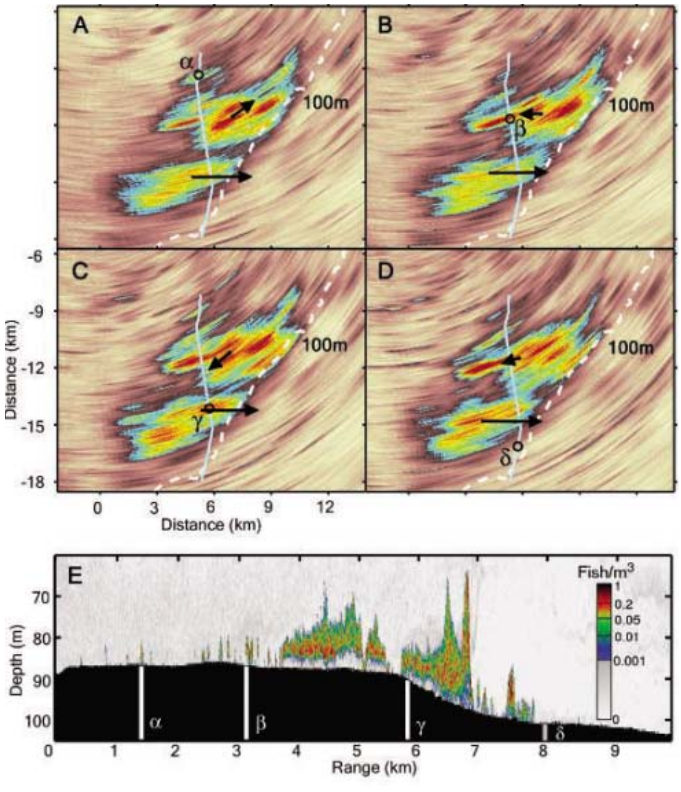

Fig. 2. A comparison of OAWRS with conventional fish-finding sonar (CFFS). (**A** to **D**) A sequence of instantaneous OAWRS areal density (fish/m²) images taken roughly 10 min apart, starting at 11:59:05 EDT on 14 May 2003, is shown. The color bar is the same as in Fig. 1. The corresponding CFFS transect is overlain in light blue, with the CFFS position for the given OAWRS image indicated by a circle. The white dashed line is the 100-m depth contour. (**E**) Range-depth profile of fish volumetric density (fish/m³) measured by CFFS along the transect shown in (A) to (D). White bars (in the lower black region below the sea floor) correspond to typical time-space points α, β, and γ, where both systems co-register dense fish groups [(A) to (C)]; the gray bar corresponds to point δ in (D), where neither system registers dense fish groups.

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missed by the conventional line-transect method (Fig. 2E), which provides no evidence that fish in the γ group are actually well connected to those previously imaged in the β group or occasionally in the α group as well.

We noticed a daily pattern in shoal behavior that involved considerable horizontal migration and thus differed substantially from the day-to-night vertical migrations previously observed with downward-directed sonar in line transects (*23*, *24*). The pattern, observed consistently in the 3 days during which we could monitor large shoals over all daylight hours, began with the horizontal consolidation of shoals in the morning, typically organized by a sharp seaward edge extending for kilometers along a bathymetric contour of the continental shelf edge. Rapid fragmentation and dispersal followed by mid-afternoon, well before sunset when vertical migration began, as shown in Fig. 3, A to D, between 14:20 and 15:00 eastern daylight time (EDT). Fragmentation predictably began with faulting at the bridges between population centers. The bridges were apparently not sufficiently strong to withstand the internal or external pressures to diverge that acted on the shoal's internal population centers.

To describe this behavior quantitatively, time series of changing fish population (Fig. 3E) were computed at very high sample rates (50-s intervals) from imagery acquired with the waveguide technology over the hundreds of square kilometers immediately encompassing the shoal. We find that total fish population (gray curve of Fig. 3E) decomposes into the sum of a temporally stable (brown curve of Fig. 3E) and a temporally unstable (blue curve of Fig. 3E) time series. The same areal fish density (ν_A) threshold (0.2 fish/m^2) that separates the temporally stable from the unstable population is also extremely effective in spatially segmenting large shoals from smaller background groups in our instantaneous wide-area images (Figs. 1; 2, A to D; and 3, A to D). The stable component comprises the widely scattered fish groups that would form the observable background scene in the absence of a large shoal. The temporally unstable component effectively characterizes the dramatically dynamic spatial-temporal fluctuations of the large shoal. We believe that fluctuations in total population are primarily due to convergences and divergences in ν_A values above and below another threshold [minimum detectable fish density (ν_0) = 0.01 fish/m^2] where seafloor scattering mechanisms begin to become important and mask fish imaging (*15*–*19*). They may also arise from fish groups entering and leaving the survey box.

Time series enable us to introduce the concept of an autocorrelation (*25*) time scale to quantitatively characterize major temporal fluctuations in shoal population. We find that the autocorrelation time scale ranges between 5 and 10 min (fig. S1A) for the very large shoal of Figs. 1A, 2, and 3, which extends for tens of square kilometers (Fig. 3F). Shoal population (blue curve in Fig. 3E) can fluctuate dramatically in these short time scales, by 20% or a few million fish. Although dramatic, the fluctuations are consistent with the roughly 1 m/s speed at which fish in a shoal typically swim (*26*–*28*), as seen from the corresponding areal changes in Fig. 3F. The frequency spectrum of shoal population (fig. S1B) shows no remarkable periodicity, but like the spatial spectrum follows a consistent power-law process that now enables quantitative statistical predictions of

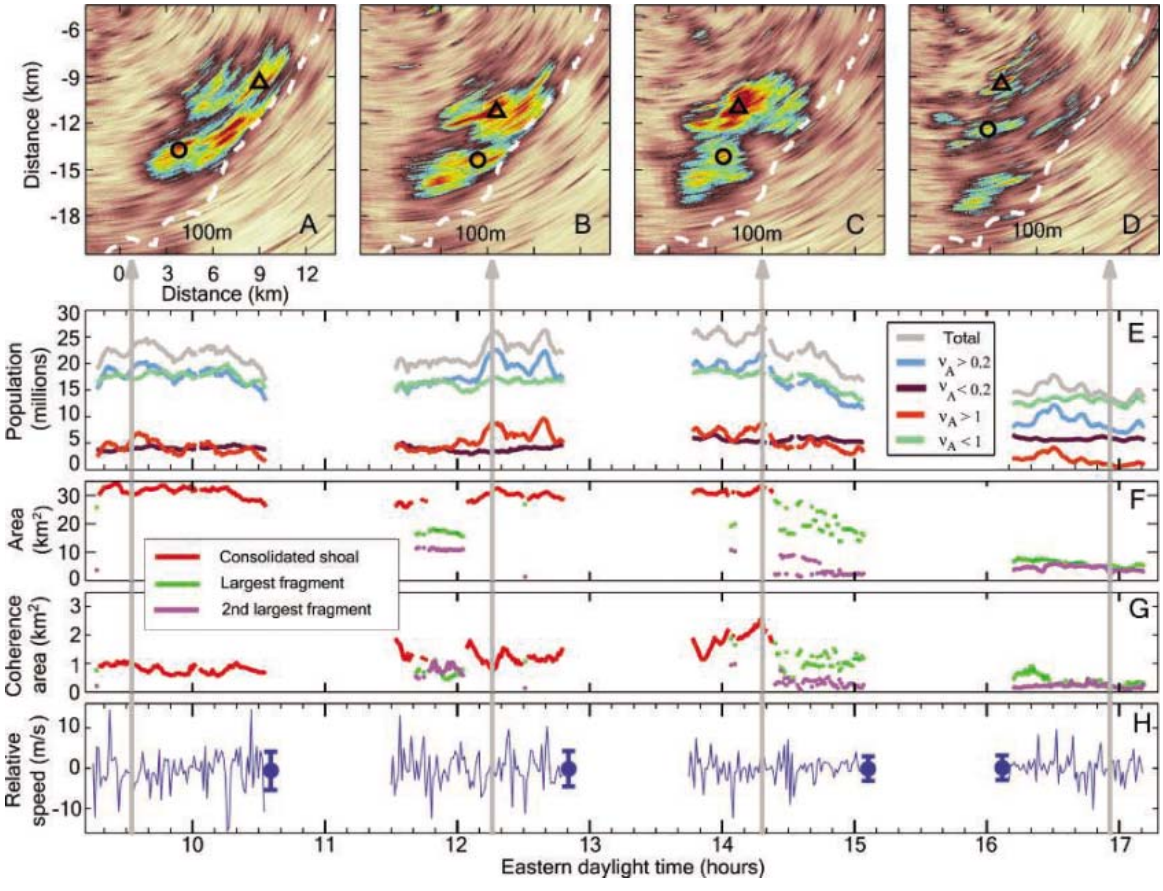

Fig. 3. Evolution of a fish shoal from morning to evening from OAWRS imagery and a time series on 14 May 2003. (**A** to **D**) Four instantaneous OAWRS images or snapshots illustrating morning consolidation and afternoon fragmentation of the shoal. The color bar is the same as in Fig. 1. Vertical arrows indicate snapshot times. (**E**) A time series of population within the area shown in (A) to (D) for ν_A within each of the thresholds specified. Gaps in the time series are due to towed-array turns. (**F**) Area occupied by a consolidated shoal or its two largest fragments for $\nu_A > \nu_{shoal} = 0.2$ fish/m^2. (**G**) The internal coherence area is the area within 1/*e* of the 2D autocorrelation peak of instantaneous OAWRS fish density within the shoal or fragment. The centroids of two particular population centers within the shoal are indicated by the circle and the triangle in (A) to (D). (**H**) Relative speeds between the centroids of the two population centers shown in (A) to (D), with mean (blue circle) and standard deviation (bars) shown for each track.

temporal behavior over wide areas and short time scales.

Shoal fragmentation and dispersal also occur very rapidly, as shown in Fig. 3E, where total population plummets in a 30-min period beginning at 14:20 EDT. More than 10 million fish disperse to below the ν_0 threshold or leave the survey box. The remaining shoal fragments contain less than half the original shoal population. This and other remotely observed depopulation events were episodic, with peak dispersal rates reaching up to 0.5 million fish/min. Indeed, very large fish shoals were often lost from the view of our conventional line-transect survey system but not from the simultaneous view of our remote-sensing system based on waveguide technology.

Structural similarity can be reexamined in a time-space context by comparing time series of a shoal's outer area (Fig. 3F) to its characteristic internal area of coherence (Fig. 3G), which is the area within which population density is relatively constant. The ratio of these gives an estimate of the number of "degrees of freedom": the independent coherence cells (*25*) or primary population centers within the shoal or within its largest fragment. The fact that this ratio remains relatively constant over time even after the shoal undergoes severe fragmentation and dispersal is further evidence of structural similarity at all spatial scales, even during such dramatic events, which is consistent with fish assembly and reassembly models (*29*). Fluctuations in the shoal's outer area tend to span only a small percentage of the total area. This is true for the inner area only during periods when the shoal is not undergoing fragmentation, as can be seen in Fig. 3, F and G. Otherwise, the inner area fluctuates rapidly, reflecting an internal turbulence that probably fragments shoals.

It is remarkable that both the total population and the internal coherence area attain maxima just before the final fragmentation and dispersal of the shoal. This coincides with the shoal's transformation into a classic hourglass pattern (Fig. 3C). In hourglass patterns, migration from one wing to the other has often been observed when the depopulating wing is under attack by predators (*7*). Although we have no evidence of such an attack on the shoal in Figs. 2 and 3, and other explanations such as feeding are possible, we do see a massing of population in the northern wing of the hourglass, with a decline of population in the southern wing. This is evident in Fig. 3C and in the subsequent time series of Fig. 3F, where the largest fragment is the northern one and the second largest is the southern one.

The waveguide technology has also revealed the internal motion and migration patterns within very large fish shoals, during time spans ranging from less than 1 min to days, as shown in the imagery sequence of Fig. 2, A to D. Fundamental questions that depend on knowing "the degree of coordination in the movements" between fish populations that were previously "nearly impossible to detect" (*6*) can now be addressed. We show that even when very large shoals are highly consolidated, densely packed, and structurally similar to small groups of fish, they do not exhibit synchronized motion over short time scales, as much smaller groups often do (*10*). The many interconnected population centers within a very large shoal have centroids that undergo local positional oscillations in the horizontal, over time scales on the order of minutes, which have no correlation with each other. This is illustrated by the image sequence of Fig. 2, A to D, where velocity vectors for two centroids within the very large shoal are effectively uncorrelated in time and space.

Part of this uncorrelated internal motion arises from fish density waves occurring regularly, every few minutes, as seen by the peak events in Fig. 3H. We identify these as waves because they exceed, by an order of magnitude, the typical speed at which fish swim (*26–28*). Such waves travel with the apparent speed of an organized sequence of locally interconnected compaction events, like the waves that people propagate in sports stadiums by standing up and sitting down in phase, rather than at the speed at which any individual moves. The waves cause relative displacements of local population centers that are bounded by the roughly 1- to 3-km internal coherence area of Fig. 3G, as can be seen by integrating the separation rate of Fig. 3H over time. Waves have been previously seen in fish shoals spanning scales up to only tens of meters, where they have been hypothesized to provide a rapid means of communication in response to predation or other pressures (*10*, *30*, *31*). The most frequent relative motions between the local population centroids, however, occur at the much lower speeds at which individual fish can swim (fig. S1C).

Fish density waves may be used to maintain organizational coherence in very large shoals. The speed, duration, inter-arrival times, and displacements associated with the peak events in Fig. 3H suggest that waves are continuously reflecting from the boundaries of the local population center where they are confined. The waves may then provide a means for individual fish to sense the spatial extent and maintain the coherence of this local subgroup. So far, however, no evidence has appeared of communication over greater distances at a rate faster than fish can swim. Instead, we have observed substantial interaction within shoals spanning tens of kilometers by both bumping and merging of population centers, as well as by population flow across bridges. The relative slowness of this means of communication may be responsible for the inability of shoals to stay together under intense external or internal stresses.

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HIV Decline Associated with Behavior Change in Eastern Zimbabwe

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Few sub-Saharan African countries have witnessed declines in HIV prevalence, and only Uganda has compelling evidence for a decline founded on sexual behavior change. We report a decline in HIV prevalence in eastern Zimbabwe between 1998 and 2003 associated with sexual behavior change in four distinct socioeconomic strata. HIV prevalence fell most steeply at young ages—by 23 and 49%, respectively, among men aged 17 to 29 years and women aged 15 to 24 years—and in more educated groups. Sexually experienced men and women reported reductions in casual sex of 49 and 22%, respectively, whereas recent cohorts reported delayed sexual debut. Selective AIDS-induced mortality contributed to the decline in HIV prevalence.

Surveillance data indicate that HIV prevalence has declined in several countries in east Africa (*1*). However, even in Uganda, the country with the most extensive evidence of a large-scale, long-term decline in HIV prevalence (*2*, *3*), controversy surrounds both the existence of a decline and its attribution to sexual behavior change (*4*–*6*). This controversy has been fed by three factors: (i) doubts surrounding the representativeness of HIV surveillance data drawn from pregnant women attending antenatal clinics at selected sites within the country (*7*); (ii) the possibility that declines in HIV prevalence could occur in the absence of the deliberate adoption of safer behaviors (*8*, *9*), i.e., as a result of saturation of infection and selective mortality within high-risk groups; (iii) a paucity of data directly linking declines in HIV prevalence to the adoption of safer sexual behaviors (*10*). Until now, there has been no evidence for decline in HIV prevalence in southern African countries (*1*).

We examined changes in HIV prevalence and sexual behavior occurring between 1998 and 2003 in Manicaland, Zimbabwe, in an open population cohort of 9454 adults recruited in two household censuses—the first conducted between July 1998 and February 2000, the second 3 years later—and concurrent changes in HIV prevalence among local antenatal clinic attendees. Patterns of mortality and new infection were explored in the closed cohort of individuals recruited at baseline. Data were collected from 12 communities enumerated in succession in four socioeconomic strata (*11*), including small towns, forestry/tea/coffee estates, roadside settlements, and subsistence farming areas. Participation rates compared well with those obtained in similar studies (table S1).

HIV prevalence in the 12 study sites was observed to decline over an average 3-year intersurvey interval from 23.0% to 20.5% [adjusted odds ratio (AOR), 0.87; 95% confidence interval (CI), 0.80 to 0.95] (table S2). HIV prevalence had declined from 19.5% to 18.2% in men aged 17 to 54 years (AOR, 0.84; 95% CI, 0.74 to 0.96) and from 25.9% to 22.3% in women aged 15 to 44 years (AOR, 0.88; 95% CI, 0.79 to 0.98). Absolute declines in HIV prevalence were recorded in all four socioeconomic strata (table S3) and in 10 of the 12 study sites (significantly more than half of the sites enumerated; $P = 0.039$).

HIV prevalence declined in men aged 17 to 34 years and women aged 15 to 29 years (Fig. 1). The decline in HIV prevalence was most pronounced in men aged 17 to 29 years, from 10.6% to 8.1% (a decline of 23%; $P < 0.01$), and in women aged 15 to 24 years, from 15.9% to 8.0% (49%; $P < 0.001$). HIV prevalence increased among respondents aged over 35 years ($P < 0.025$) (table S2). The age pattern of change in HIV prevalence is consistent with one that occurs through the natural dynamics of an HIV epidemic (*12*), but the quantum of the declines recorded in younger age groups, over a relatively short 3-year period, and the concentration of the decline among people with secondary school education (*13*) strongly suggested a contribution of sexual behavior change (*3*). Through the phased sampling, it was possible to see that the change in HIV prevalence occurred consistently over time (table S3).

Surveillance data from local antenatal clinic attendees indicated modest declines in HIV prevalence overall (21.1% to 19.2%; AOR, 0.87; 95% CI, 0.71 to 1.06) and at young ages (fig. S1). HIV prevalence in young pregnant women is lower than in women in the general population, owing to the reduced fertility of HIV-infected women (*14*).

Overall, HIV prevalence increased over time among individuals seen at baseline (i.e., members of the closed cohort). The contributions of mortality and new HIV infections to changes in HIV prevalence observed in the closed cohort are shown in Fig. 2 and table S4. HIV incidence was highest in men aged 20 to 44 years and women aged 15 to 29 years. Mortality among all uninfected individuals was low (less than one death per 100 person-years). As in other populations without access to antiretroviral treatment (*15*), the risk of death was an order of magnitude greater for HIV-infected men (relative risk, 11.3) and women (relative risk, 9.6). Mortality is greater and is concentrated at older ages in HIV-infected men than in HIV-infected women. These patterns reflect the older male average age at infection, which is caused by a combination of less risky early-age sexual activity and the lower female-to-male than male-to-female HIV transmission probability (*16*), and results in faster disease progression (*17*). In addition, the spread of infection may have occurred earlier in men (*18*).

Within the closed cohort, HIV prevalence increased in younger people (men aged 18 to 26 years and women aged 15 to 23 years at baseline), for whom HIV incidence was high (approximately 3%) and mortality in infected individuals was relatively low. In the older age groups (men aged 35 to 54 years and women aged 30 to 44 years at baseline), HIV prevalence fell, owing to high mortality in infected individuals and moderate levels of HIV incidence.

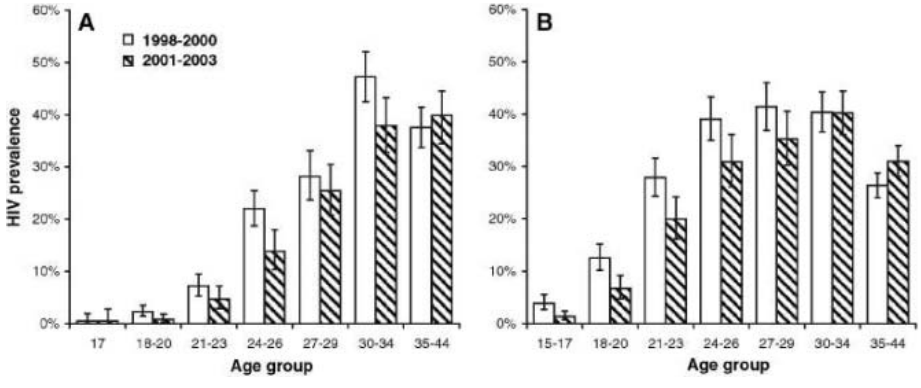

Fig. 1. Change in HIV prevalence by age group over a 3-year intersurvey period from 1998–2000 to 2001–2003, Manicaland, Zimbabwe. (**A**) Men. (**B**) Women. Error bars, 95% CIs around sample means.

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When the effective reproductive number, R_t (the number of secondary infections arising from each primary infection at time t in an HIV epidemic), is less than 1, an HIV epidemic is in a period of decline (*11*). The data yielded approximations for R_t of 0.57, 0.73, 0.48, and 0.49 for the town, estate, roadside, and subsistence farming populations, respectively.

For both men and women, the reported number of lifetime sexual partners in the baseline survey was strongly associated with HIV infection (*19*). In the cohort of sexually active individuals uninfected at baseline, HIV incidence was higher in those who reported multiple sexual partners during the 3-year intersurvey period than in those who reported a single partner [men: adjusted hazards ratio (AHR), 1.82; 95% CI, 1.17 to 2.85; women: AHR, 3.35; 95% CI, 2.13 to 5.27]. The risk rose progressively with increasing number of sexual partners reported for women (AHR, 1.14; 95% CI, 1.07 to 1.21) but not for men (fig. S2). For men, consistent condom use in casual partnerships lessened the risk of HIV infection (AHR, 0.38; 95% CI, 0.15 to 0.99). These data, along with the extremely low HIV prevalence in teenagers, the rapid increase in prevalence from age of sexual debut, and an absence of association between recent receipt of medical injections and incident HIV infection (*6*, *20*), indicate that HIV in Zimbabwe is transmitted primarily through heterosexual sex.

We found evidence for a delay in onset of sexual activity among teenage men and women, and for reductions in the proportions of sexually experienced men and women engaging in casual sexual relationships (Fig. 3A, fig. S3, and table S5). At baseline, 45% of 17- to 19-year-old men reported having commenced sexual activity; 3 years later, 27% of the same age group reported having started sexual activity (AHR, 0.55; 95% CI, 0.46 to 0.66). Over the same period, the percentage of 15- to 17-year-old women who reported sexual experience fell from 21% to 9% (AHR, 0.48; 95% CI, 0.36 to 0.63). Among those who had started sex, the proportion of men reporting a recent casual partner fell by 49% (25.9% versus 13.2%; $P < 0.001$); the decrease for women was not statistically significant (7.5% versus 5.9%; $P = 0.292$). Consistent condom use with recent casual partners remained at quite a high level in men (41.6% versus 42.2%) and increased in women (36.5% versus 26.2%; $P = 0.003$). There was no evidence for an increase in consistent condom use with regular partners. For each sex, there were statistically significant ($P < 0.05$) reductions in reported numbers of new sexual partners in the previous year (Fig. 3B), sexual partners in the previous month, and current sexual partners (table S5) (*11*).

Data on high-risk sexual behavior can be underreported (*21*), a tendency that may increase over time in an HIV epidemic. Caution is therefore needed in interpreting these results (*11*). Furthermore, when considering the impact of changes in sexual behavior on an HIV epidemic at the population level, it is important to recognize the contribution of selective AIDS-

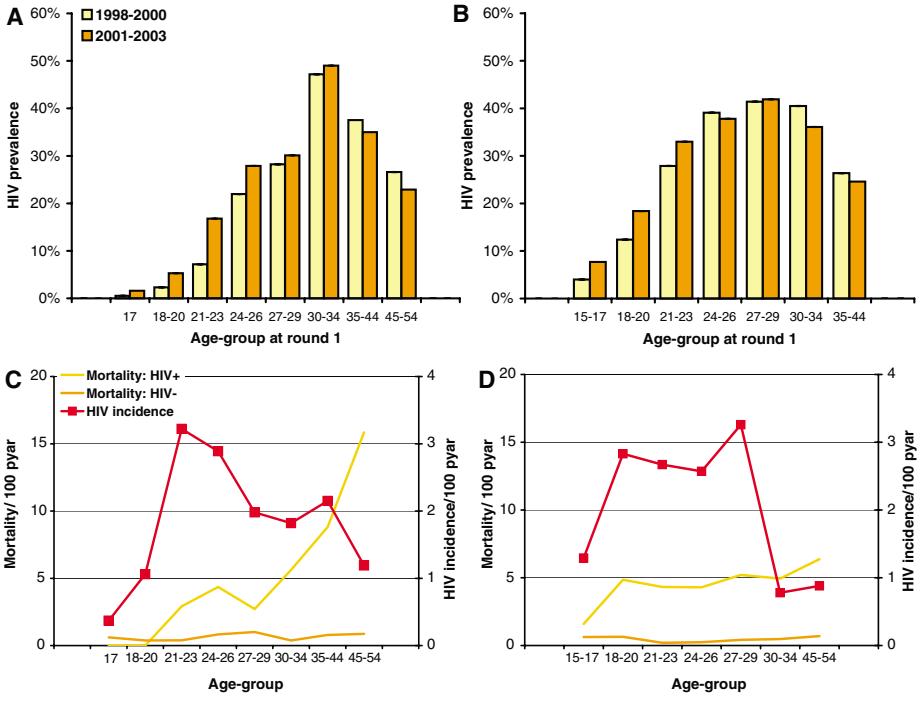

Fig. 2. Components of change in HIV prevalence in members of the closed cohort of 4320 men and 5134 women recruited at baseline, over a 3-year intersurvey period from 1998–2000 to 2001–2003, Manicaland, Zimbabwe. (**A** and **B**) Change in HIV prevalence, by age group at baseline interview, for (A) men and (B) women. (**C** and **D**) Mortality rates by HIV infection status at baseline (left *y* axis) and HIV incidence in persons uninfected at baseline and retested at follow-up (right *y* axis) for (C) men and (D) women.

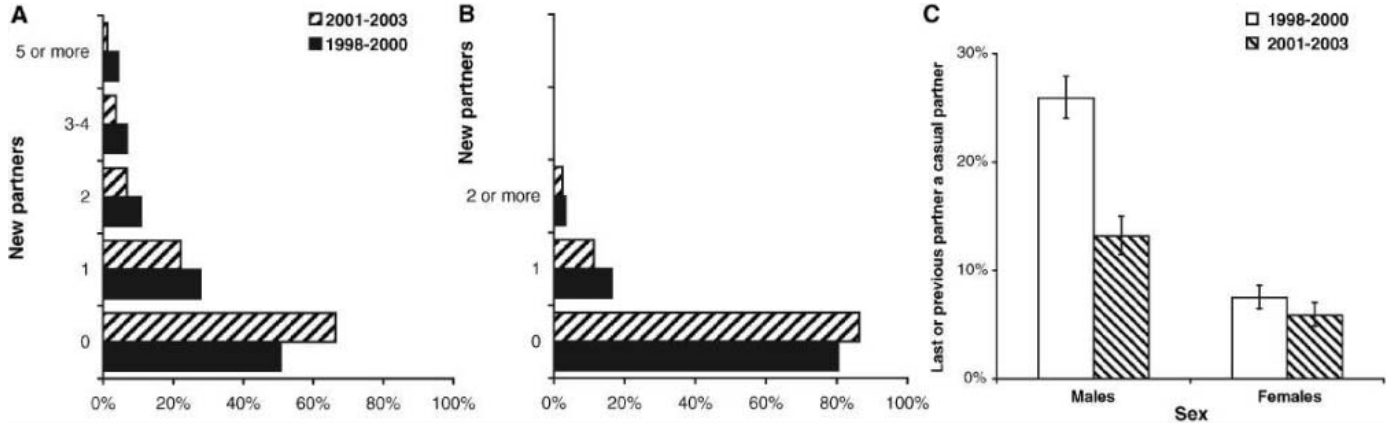

Fig. 3. Comparison of sexual behaviors reported at baseline (1998 to 2000) and follow-up (2001 to 2003) in an open cohort survey, Manicaland, Zimbabwe. (**A** and **B**) Distributions of number of new sexual partners in the previous year for (A) men and (B) women. (**C**) Percentages of men and women (with 95% CI) who reported that at least one of up to two most recent sexual partners in the previous month was a casual partner.

induced mortality (*22*). Death rates are particularly high in individuals with high numbers of lifetime sexual partners, and their death decreases the variance in reported numbers of sexual partners. This in turn, alters the sexual network through which HIV infection spreads within the population (*23*), for example, by forcing young women disposed toward forming relationships with older men to choose younger partners or abstain. In the current study, the individuals who died during the intersurvey period had reported higher numbers of lifetime sexual partners at baseline than those who survived to be reinterviewed (men: mean, 13.6 versus 8.7, $P = 0.001$; women: mean, 3.0 versus 2.0, $P < 0.001$). Given the relatively small numbers of individuals who died, AIDS-associated mortality explained only 6.3% of the observed reduction in sexual partner change in men and 8.6% in women, but it cannot be discounted as an important long-term factor.

Selective migration of individuals with high levels of HIV infection could also contribute to changes in HIV prevalence and associated sexual behavior measured at the population level. High numbers of young adults migrated from our study areas to search for employment (*11*). However, we found no differences in HIV prevalence or sexual risk behavior between migrants and residents at baseline (*24*). By contrast, there was a lower HIV prevalence among recent migrants into the study areas at follow-up than at baseline (AOR, 0.62; 95% CI, 0.50 to 0.77), which contributed to the observed decline in prevalence (table S3).

HIV prevalence in eastern Zimbabwe is similar to national estimates (*25*), and the decline occurred equally in areas with and without focused interventions (table S3). Furthermore, the trends in HIV prevalence in women attending antenatal clinics in our study areas mirror those seen nationally in recent surveillance data (*11*). Thus, these data support the interpretation that HIV prevalence in the general population in Zimbabwe has begun to decline.

Owing to the long average incubation period of HIV infection, HIV prevalence reflects the accumulation of infections over a period of more than 10 years and is insensitive to behavior change. A change in behavior can precede any observed decline in HIV prevalence and would explain the absence of concurrent reductions in HIV incidence in Uganda when HIV prevalence fell during the late 1990s (*9*). Indeed, behavior change may have been most rapid in Uganda in the early 1990s when HIV prevalence first began to decline (*3*). If so, Uganda could provide a model for the pattern of change now seen in Zimbabwe. Our data suggest that the changes in behavior occurring in Zimbabwe are similar to those underpinning the long-term decline in HIV prevalence in Uganda, i.e., a delay in age at first sex and a reduction in casual sex (*5*), but that consistent condom use with casual partners has also contributed.

Given the stage of the HIV epidemic (*26*), fear of AIDS mortality may have influenced behavior (*22*). Zimbabwe's well-educated population (*27*) and good communications and health service infrastructure could have facilitated HIV prevention (*13*). HIV prevention activities in Zimbabwe (*28*) have included early control of sexually transmitted infections, social marketing of condoms, voluntary counseling and testing services (*26*), television and radio serial dramas, and the activities of the Zimbabwe National AIDS Trust Fund (*29*).

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Rats Smell in Stereo

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It has been hypothesized that rats and other mammals can use stereo cues to localize odor sources, but there is limited behavioral evidence to support this hypothesis. We found that rats trained on an odor-localization task can localize odors accurately in one or two sniffs. Bilateral sampling was essential for accurate odor localization, with internasal intensity and timing differences as directional cues. If the stimulus arrived at the correct point of the respiration cycle, internasal timing differences as short as 50 milliseconds sufficed. Neuronal recordings show that bulbar neurons responded differentially to stimuli from the left and stimuli from the right.

Rats use olfactory cues to locate and identify objects in their environment (*1*, *2*). Odor sources can be localized by one of two broad mechanisms (*3*): sequentially comparing odor concentrations at two different locations (*4*) or comparing simultaneous samples from two different locations of the body (*5*–*7*). The latter strategy requires separate sampling and parallel neuronal pathways that eventually converge for bilateral comparison. Rat nostrils are about 3 mm apart and at first sight appear to be too close to each other to support separate sampling. However, studies of respiratory airflow patterns have shown that air flow is directed laterally to the left and right of the respective nostrils, which suggests that separate sampling of the olfactory environment may occur (*8*). Further, the two nasal passages are almost completely isolated from each other and supply two distinct sheets of olfactory sensory epithelia. The axonal projections from the sensory epithelium maintain this separation into the first olfactory

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region of the brain, the olfactory bulb. Higher olfactory cortical areas are sites of bilateral convergence. Consistent with this bilateral convergence, neurons in the anterior piriform cortex have been shown to respond differentially to ipsilateral, contralateral, or bilateral odor stimulation (*9*). Thus, the olfactory system of the rat appears to satisfy the two requirements of separate sampling and neuronal mechanisms for stereo odor localization. We therefore tested the hypothesis that rats localize odor sources using stereo cues.

Using standard behavioral conditioning procedures, we trained water-deprived rats to localize the source of an odor to the left or to the right. Each rat initiated a trial by poking its nose into a sniff port. After a random interval of 0 to 100 ms, an odor stimulus was delivered on either the left or the right. Rats received water rewards for licking at one of two water spouts: the left water spout for a left odor trial and the right water spout for a right odor trial. Rats performed 100 to 200 trials per session, and one session per day, for consecutive days except weekends. Figure 1A shows the four stages of a trial: nose poke, odor onset, nose withdrawal, and lick. The odor stimulus of intensity 1% of saturated vapor was produced using a custom-made air-dilution olfactometer. Air flow was maintained at 5 liters/min on both sides throughout a session. Each of the rats was trained on one of three odors: isoamyl acetate, 1-4 cineole, or phenethyl alcohol.

We trained 14 Wistar rats (12 male and 2 female) to a performance criterion of 80% accuracy per session on the odor-localization task (Fig. 1B). Figure 1, C and D, shows the distribution of odor sampling times and movement times for one rat over five sessions. Median odor sampling times for individual training sessions were in the range of 280 ms to 400 ms (*10*).

To ensure that the rats used only odor cues to solve the task, we performed a number of controls to address other cues: (i) Absolute intensity differences. We tested the rats with the left and right odor channels interchanged. Their performance was not affected by this change ($n = 5$). (ii) Sound cues. We tested the rats with no flow through the odor bottles, although the sound cues due to valve switching remained. Performance of the rats dropped to chance levels ($n = 5$). (iii) Flow rate changes as somatosensory cues. Odor onset was associated with a 1% change in total air-flow rate. It has been hypothesized that air flow can be detected by the whiskers (*11*). We trimmed the anterior sets of whiskers and found that this did not affect the performance of the rats ($n = 6$). Further, differences of 1% in flow between the two sides were smaller than the error range of the flow meters and so are unlikely to be consistent cues. (iv) Air-flow transients. Air-flow transients and pressure pulses propagate at the speed of sound, whereas the odor itself propagates at the speed of the air flow in the tubes (~7 m/s). We tested the rats ($n = 6$) with longer odor tubes connected to the behavior box and found a significant increase in sampling time that matched our estimates of air-flow rates (ANOVA, $P < 0.05$) (fig. S2). We also tested the rats on sessions where odor was already present on one of the sides before a nose poke, thus eliminating transients ($n = 5$). Rats performed above criterion on such sessions. Figure 1E shows the accuracy of the rats on the different control sessions.

We then implanted thermocouples in the nostrils of three of the rats to monitor respiration in terms of temperature changes in inhaled and exhaled air (fig. S3). Similar to earlier studies (*12*, *13*), we found that rats typically sniffed at 7 to 8 Hz during odor sampling (fig. S3). Odorant direction discrimination was complete within two to three sniffs on most trials (Fig. 1F). We recorded odor onset as the time of application of a switching signal to the electronic valve controlling odor flow. Therefore, the above sampling times include the time taken for the odor to reach the rat. We estimate that the odor takes ~80 to 100 ms to reach the rat after the switching signal (*14*). Taking this into account, our results suggest that rats localize odor sources accurately, with odor sampling times of ~250 ms, within one to two sniffs.

To determine whether the rats were using stereo cues to localize the source of the odor, we disrupted bilateral odor sampling by stitching one of the nostrils shut (Fig. 2A). The measurements started after rats performed at criterion

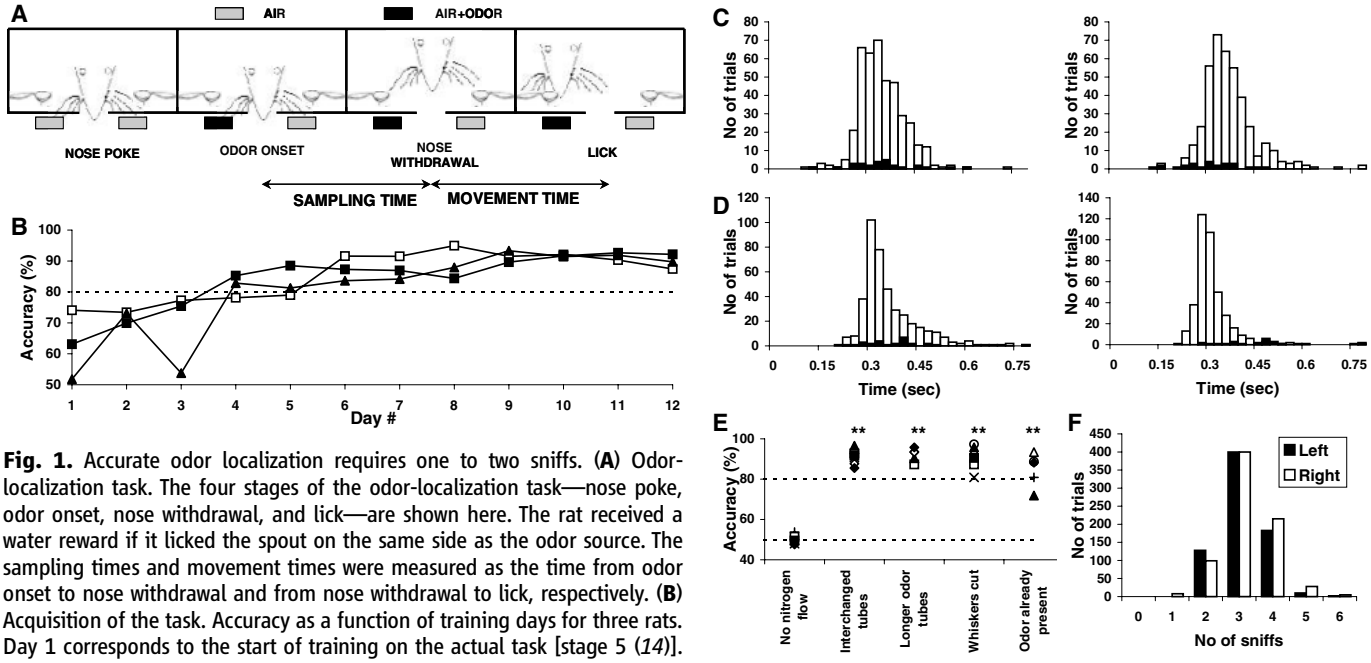

Fig. 1. Accurate odor localization requires one to two sniffs. (**A**) Odor-localization task. The four stages of the odor-localization task—nose poke, odor onset, nose withdrawal, and lick—are shown here. The rat received a water reward if it licked the spout on the same side as the odor source. The sampling times and movement times were measured as the time from odor onset to nose withdrawal and from nose withdrawal to lick, respectively. (**B**) Acquisition of the task. Accuracy as a function of training days for three rats. Day 1 corresponds to the start of training on the actual task [stage 5 (*14*)]. (**C**) Distribution of sampling times over five sessions for one rat performing the task with isoamyl acetate as the odor. The sampling times for the left-side odor trials and right-side odor trials are shown separately. The empty bars indicate correct trials, and the filled bars indicate error trials. The median sampling times for the left and the right were 314.8 ms and 332.6 ms, respectively. (**D**) Distribution of movement times for the same rat. The median movement times for the left and the right were 316.8 ms and 280.9 ms, respectively. (**E**) Accuracies of the rats on different controls. These control sessions were randomly performed between days with normal sessions. All the days were significantly different from the "No nitrogen flow" control session (**, ANOVA, $P < 0.0005$). (**F**) Number of sniffs taken during left and right odor trials for two thermocouple-implanted rats (five sessions for each rat). Tubing delays account for ~100 ms, or about 1 sniff.

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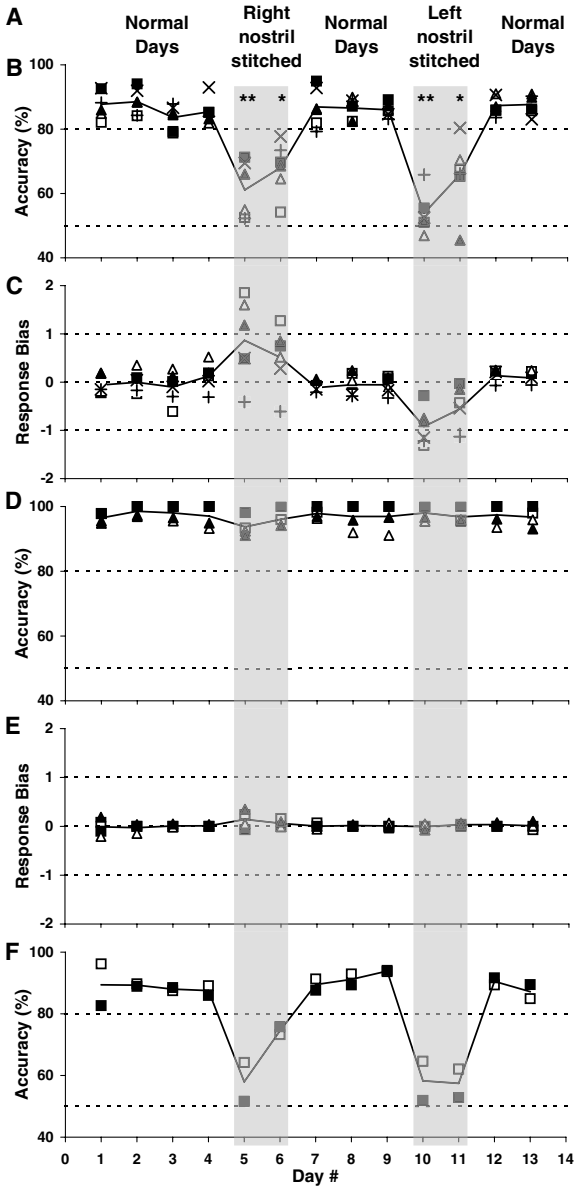

Fig. 2. Bilateral odor sampling is essential for accurate odor localization. (**A**) Experimental design. In all of these plots, the shaded region depicts the days on which one of the nostrils was stitched. The black line represents average values, and each symbol represents an individual rat. Nostril stitching was a 10-minute procedure done under anaesthesia. (**B**) Accuracy on the odor-localization task (filled symbols and +, isoamyl acetate rats; open symbols and X, 1-4 cineole rats). The first day of stitching in both cases was significantly different from the normal days (**, ANOVA, $P < 0.0005$), and the second day was significantly different from the normal days (*, ANOVA, $P < 0.05$). (**C**) Response bias on the odor-localization task. Symbols for individual rats are the same as in (B). Response bias was calculated as described in (*21*). A response bias of +2 indicates that the rat licked on the left for all the trials, and a response bias of −2 indicates that the rat licked on the right for all the trials. Response bias was not significantly different throughout as different rats adopt different strategies. (**D**) Accuracy on the odor-discrimination task. In this odor-discrimination task, one of two odors was delivered from either of the sides in the same apparatus. Rats were rewarded for licking on the left side for one of the odors and on the right side for the other odor, irrespective of the direction of the odor. Accuracies were not significantly different on any of the days. (**E**) Response bias on the odor-discrimination task. Response bias was not significantly different for any of the days. (**F**) Accuracy for two rats localizing phenethyl alcohol, a pure olfactory stimulant.

for several days. Performance was monitored in training sessions for 13 days. On days 5 and 6 the right nostril was blocked by stitching, and on days 10 and 11 the left nostril was blocked. Nostril blocking and unblocking were done in a 10-min surgical procedure under anaesthesia immediately after the training session on the preceding day. Training sessions immediately before, during, and immediately after the nostril-stitching procedure were always on consecutive days. Stitches reliably blocked air flow through the nostril on the first day of stitching (*14*). For some of the rats, stitches only partially blocked air flow on the second day.

Figure 2B shows the accuracy of six rats that were used for the stitching experiments. Performance drops significantly below criterion when either of the nostrils is stitched shut and recovers immediately after removal of the stitches. The responses of most rats were biased to the unstitched side when one of the nostrils was stitched shut (Fig. 2C).

To exclude the possibility that poor performance could be a result of discomfort due to stitching, we trained two rats to perform a forced choice task where the identity, not the direction, of the odor was the cue. The rats were required to lick on the left water spout for one of the odors and lick on the right water spout for the other odor, irrespective of the side on which the odor was delivered. Performance on this task was not affected when one of the nostrils was stitched shut (Fig. 2D). In addition, the stitched rats did not exhibit any significant response bias (Fig. 2E).

The nasal cavity is innervated both by olfactory sensory neurons and by the ethmoid branch of the trigeminal nerve. The trigeminal nerve senses irritation and is activated by most, but not all, odorants at high concentrations. Studies on odor localization in humans have provided mixed results. Although von Békésy suggested that humans could use stereo cues (*15*), others suggested that only odorants that stimulated the trigeminal nerve could be localized effectively (*16*, *17*). A recent study has provided evidence that, under controlled conditions, humans can localize pure olfactory stimulants (*18*). To determine whether rats could localize pure olfactory stimulants, we used phenethyl alcohol, an odorant that does not stimulate the rat trigeminal nerve (*19*), for two of the rats (Fig. 2F). Rats successfully localized phenethyl alcohol and required bilateral sampling for accurate localization.

The above results suggest that rats can use stereo cues to localize odor sources. By analogy with the auditory system (*20*), internostril intensity and timing differences are candidate stereo cues. In a modified task, odor was present on both sides, with the onset of odor on one side leading the onset of odor on the other side by a fixed interval (Fig. 3A). Rats were rewarded for choosing the side on which onset of odor occurred first. To avoid possible odor quality differences, we designed the olfactometer to use the same odor bottle for both sides. Therefore, the odor intensity dropped by half on the first side after the onset of odor on the other side (Fig. 3A). Thus, this task presented a brief intensity difference cue along with the timing difference cue. Alternatively, the task can be thought of as a unilateral stimulus followed by a bilateral masking stimulus after a fixed interval. In a given session, trials with intervals of 0, 25, 50, 100, and 150 ms were randomly interleaved. Performance on this task was above criterion for 100-ms and 150-ms intervals. We plotted the fraction of responses on the left side as a function of the interval between onsets of odor on both sides, negative intervals implying that onset of odor on the right side occurred first (Fig. 3B). These data were fitted to a psychometric function, a function that measures stimulus detectability as a function of small changes in stimulus quality. A threshold interval of 125 ms for performance above 80% was calculated from this function as the smallest interval that corresponded to 80% accuracy (Fig. 3B).

Because the time scales of neuronal circuits are typically faster than 125 ms, we wanted to see whether this threshold for accurate performance was a result of intermittent sampling due to respiration. We used the thermocouple-implanted rats to determine the phase of respiration at which the odor first arrived in the interval task. We divided the respiration into five phases and computed response accuracy for each phase and each interval (Fig. 3C). Accuracies for the longer intervals showed little dependence on respiration phase, whereas accuracies for the shorter intervals (25 and 50 ms) were dependent on respiration phase. Accuracies in some bins reached close to criterion levels even for these

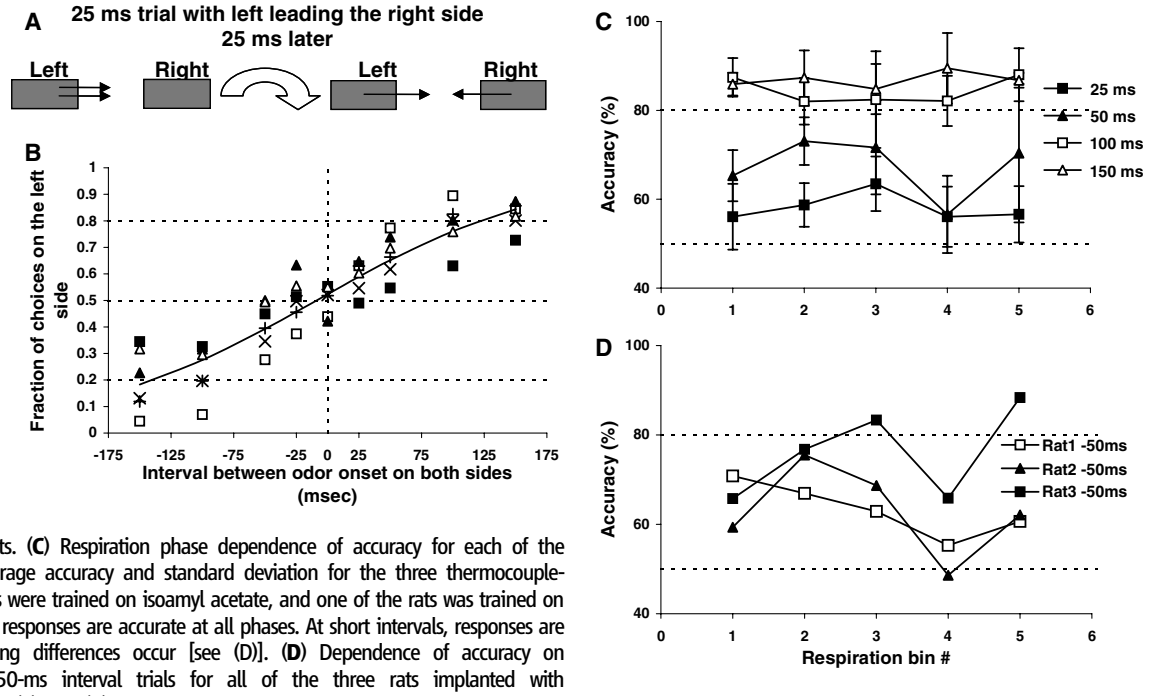

Fig. 3. Internostril intensity and timing differences can be used as cues. (**A**) Experimental design. We used the same bottle to deliver odor on both the left and the right to avoid qualitative differences. This meant that the interval task presented a brief intensity difference along with the timing difference. (**B**) Response to odor timing differences. Each symbol depicts the accuracies of one rat ($n = 6$) on the different intervals used in the interval task. The black line represents the psychometric function that was fit to the average of all the rats. (**C**) Respiration phase dependence of accuracy for each of the intervals. The plot shows average accuracy and standard deviation for the three thermocouple-implanted rats. Two of the rats were trained on isoamyl acetate, and one of the rats was trained on 1-4 cineole. At long intervals, responses are accurate at all phases. At short intervals, responses are phase dependent and binning differences occur [see (D)]. (**D**) Dependence of accuracy on respiration phase for the 50-ms interval trials for all of the three rats implanted with thermocouples. The first bin in (C) and (D) corresponds to the beginning of inhalation.

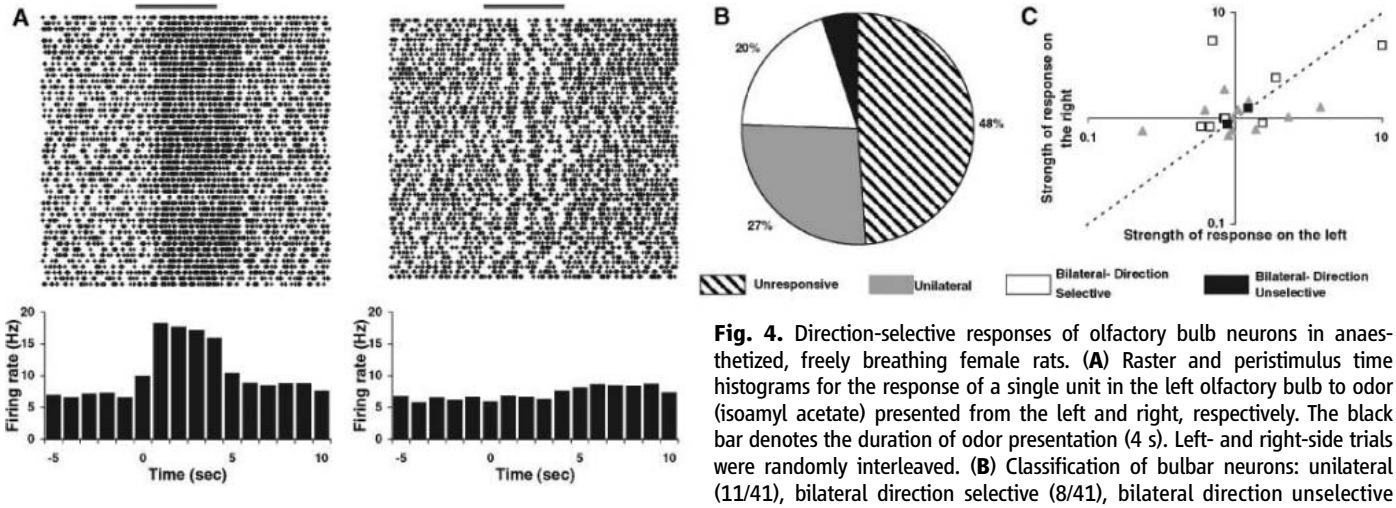

Fig. 4. Direction-selective responses of olfactory bulb neurons in anaesthetized, freely breathing female rats. (**A**) Raster and peristimulus time histograms for the response of a single unit in the left olfactory bulb to odor (isoamyl acetate) presented from the left and right, respectively. The black bar denotes the duration of odor presentation (4 s). Left- and right-side trials were randomly interleaved. (**B**) Classification of bulbar neurons: unilateral (11/41), bilateral direction selective (8/41), bilateral direction unselective (2/41), and unresponsive (20/41). Unilateral neurons showed significant firing-rate changes during odor (as compared with a preceding air period of the same duration, ANOVA, $P < 0.05$) only for odor from one of the sides. Bilateral neurons showed significant firing-rate changes in response to odor from either of the sides. Further, bilateral direction-selective neurons showed significant differences between the two odor periods (left and right, ANOVA, $P < 0.05$) (**C**) Distribution of direction selectivity. Strength of response (defined as firing rate during odor from specified direction/firing rate during preceding air period) on the right is plotted against strength of the response on the left for the responsive neurons. A log-log scale has been used. The 45° dashed line represents a lack of odor direction selectivity.

short intervals (Fig. 3D). Thus, taking into account the sampling constraints imposed by respiration, intervals as short as 50 ms can be used efficiently for localization of odor sources.

What is the neuronal substrate for odor localization? If our interpretation of separate air sampling from the two nostrils is correct, then the distinct sensory neuron projections to the olfactory bulb should result in unilateral olfactory responses. More complex responses may arise because there are feedback projections to the bulb, as well as reciprocal inhibitory projections from the contralateral bulb, routed through the anterior olfactory nucleus.

Using tetrodes, we recorded from single units in the main olfactory bulb of anaesthetized female rats. We presented odor from either the left or the right in a randomly interleaved sequence, using the same olfactometer used for the behavior. Figure 4A shows the spike rasters and peristimulus time histograms for the response of a neuron in the left olfactory bulb, sorted by odor direction. Response significance was calculated by comparing firing rate during the odor period to the immediately preceding air period of the same duration. Twenty-one of 41 neurons showed a significant response to isoamyl acetate (one-way ANOVA, $P < 0.05$). Fifty-two percent of the responsive neurons (11/21) were unilaterally responsive, that is, they showed significant firing-rate changes to odor from one side only. Eighty percent (8/10) of the remaining, bilaterally responsive neurons were direction selective and exhibited significantly different spike rates during the left and right odor periods

(one-way ANOVA, $P < 0.05$) (fig. S7). Overall, our recordings suggest that more than 90% of the responsive neurons in the olfactory bulb respond differentially to stimuli presented on the left or the right (Fig. 4, B and C). This could possibly provide a substrate for the nostril-specific activation seen in the olfactory cortex in a recent study on humans performing an odor-localization task (*18*).

Our behavioral and recording results provide constraints on the neuronal mechanisms mediating stereo olfaction: (i) We show that odor localization can use stereo cues, implying bilaterally distinct neuronal pathways. This is supported by our recordings. (ii) Direction discrimination can be made within one sniff (125 ms), implying that the brain is performing a simultaneous rather than sequential comparison. (iii) The underlying neuronal circuits appear to be able to perform the discrimination more rapidly (50 ms) but are limited by the physiological sampling rate imposed by sniffing.

von Békésy reported that humans can localize odor sources using stereo cues (*15*) but estimated a timing selectivity of 100 μs, which is three orders of magnitude smaller than what we see in rats. Based on our estimates of ~100-ms timing discrimination and an effective spacing of ~1 cm between the air-sampling regions for each rat nostril, odor plumes can be localized if they traverse the nostrils at less than 10 cm/sec. Relatively laminar air flow may lead to more sustained gradients that the rat may be able to track, through stereo sampling, to an upstream odor source. Stereo localization in a single sniff is at least twice as fast as sequential sampling, which may be important both for foraging and for predator avoidance. We suggest that, for a rat, each sniff is a perceptually complete snapshot of the olfactory world, including both odor identity (*12*) and stereo-based location.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/311/5761/666/DC1
Materials and Methods
Figs. S1 to S7
References
Movie S1

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A Cortical Region Consisting Entirely of Face-Selective Cells

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Face perception is a skill crucial to primates. In both humans and macaque monkeys, functional magnetic resonance imaging (fMRI) reveals a system of cortical regions that show increased blood flow when the subject views images of faces, compared with images of objects. However, the stimulus selectivity of single neurons within these fMRI-identified regions has not been studied. We used fMRI to identify and target the largest face-selective region in two macaques for single-unit recording. Almost all (97%) of the visually responsive neurons in this region were strongly face selective, indicating that a dedicated cortical area exists to support face processing in the macaque.

Lesion studies show that object recognition depends on the temporal lobe (*1*), but the principles of temporal lobe organization underlying the representation of objects remain uncertain. In particular, the question of how face processing is functionally organized has been a focus of intense debate (*2*–*4*). In humans, several cortical regions have consistently been found in fMRI studies to be more responsive to faces than to other objects, and it has been suggested that the fusiform face area (FFA) is exclusively dedicated to face processing (*5*). However, physiologists who are recording from the macaque temporal lobe have never found any entirely face-selective region; instead, they have reported scattered clusters of face-selective cells, especially prevalent in the upper and lower banks of the superior temporal sulcus (STS), with, at most, 20 to 30% of the cells in any region being face selective (*6*–*9*).

It is possible that an area consisting entirely of face-selective cells exists in the macaque and has simply been missed because of single-unit sampling limitations. Alternatively, no such area may exist, and regions of the macaque brain identified by fMRI as face-selective (*10*, *11*) may actually contain a mixture of cells selective for both faces and nonface objects. fMRI measures average blood flow within sampling units containing hundreds of thousands of cells, and therefore it cannot directly address the selectivity of single units. To clarify the neural organization of face processing, we used fMRI to target single-unit recordings to the middle macaque face patch. Our goal was to understand the selectivity of single neurons within this specific ~16-mm^2 (*12*) region of the temporal lobe, which appears to be topographically homologous to the human FFA (*10*).

Single-unit recordings targeted to fMRI-identified face-selective regions were performed in two monkeys, M1 and M2, in a standard electrophysiology setup outside the scanner. We first localized the face-selective regions in both monkeys with fMRI (Fig. 1, A and B), and we then implanted a recording cylinder roughly over the targeted region. A second anatomical scan with magnetic resonance (MR)–visible markers in a grid inside the recording cylinder showed precisely which grid holes in the chamber targeted the center of the face patch (Fig. 1C). Recordings were made from three adjacent grid-hole positions in both monkeys. A guide tube was placed in the grid hole to allow reliable access to the face patch.

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We used fMRI to identify face patches. Ninety-six images of faces, bodies, fruits, technological gadgets, hands, and grid scrambled patterns (16 images per category, one category per block; see fig. S1 for example stimuli) were presented to the monkey during continuous central fixation. To optimize the signal-to-noise ratio, we used the exogenous iron oxide contrast agent MION (monocrystalline iron oxide nanoparticle) (*13*). Consistent with previous results (*10*, *11*), in both monkeys several discrete regions (face patches) responded significantly more to faces than to five other object categories. The most prominent face patch in both monkeys was the one located at A6 (i.e., 6 mm anterior to the interaural line) (Fig. 1, A and B). In addition, monkey M1 had a more posterior face patch located at A0, and both monkeys had anterior face patches located between A15 and A22 (fig. S2). We designate the patch located at A6 the "middle face patch" throughout this paper, to distinguish it from the anterior face patches and from the region posterior to A6, which showed variable face selectivity across monkeys.

Figure 1A shows a semisagittal section from monkey M1 in which all three face patches are visible. We targeted the middle face patch for single-unit recordings because it was the most prominent in both monkeys (and in all the monkeys we have scanned so far, $n = 7$ monkeys) and because of its possible homology to the human FFA (*10*). In monkey M1, this patch was located on the lip of the lower bank of the STS; whereas in monkey M2, it was located in the fundus of the STS (Fig. 1B). This individual difference underscores the importance of using fMRI to target single-unit recordings in the same animal. The lesion left by the recording guide tube in monkey M1 is visible in Fig. 1, A and C, and confirms, in three dimensions, that our single-unit recordings accurately and precisely targeted the middle face patch.

We tested the face selectivity of 405 single units (241 in the right hemisphere of monkey M1 and 164 in the left hemisphere of monkey M2) in the middle face patch with the same 96 images used to localize the face patches with fMRI. The stimuli were presented foveally every 400 ms (200 ms on and 200 ms off) in random order for 4 to 10 repetitions while the monkey fixated. We recorded responses from all single units encountered, regardless of visual responsiveness or face selectivity. Across the population of recorded cells, 182 of 241 (76%) cells in monkey M1 and 138 of 164 cells (84%) in monkey M2 gave significant responses (*14*) to at least one of the 96 images and were therefore classed as visually responsive.

Figure 2A shows the normalized response selectivity of all visually responsive cells recorded from the two monkeys (*15*). Each of the faces (images 1 to 16) elicited stronger responses across the population than did any of the 80 nonface objects (images 17 to 96). Figure 2B shows bar graphs of the average responses to each of the 96 images across the population of visually responsive cells. In monkey M1, the ratio of face to nonface object response was −74 (negative, due to a small suppression to the nonface objects on average); in monkey M2, this ratio was 21.

In addition to the overwhelming bias for face stimuli, many cells gave significant responses to a few particular nonface objects (the faint orange lines in Fig. 2A to the right of the first 16 columns). In monkey M1, the two nonface objects that gave mean responses across the population exceeding six average standard errors (SEs) were a clock and an apple (Fig. 2C). In monkey M2, the only nonface objects that elicited significant responses across the population were also round. The small but significant responses to round stimuli suggest that the coding of faces in the middle face patch is based on analysis of visual shape.

To quantify the face selectivity of individual cells, we defined a face-selectivity index as FSI = (mean response$_{faces}$ − mean response$_{nonface\ objects}$)/(mean response$_{faces}$ + mean response$_{nonface\ objects}$). Figure 2D shows population histograms of the FSI in both monkeys. The distributions are strongly skewed toward high FSI values. The

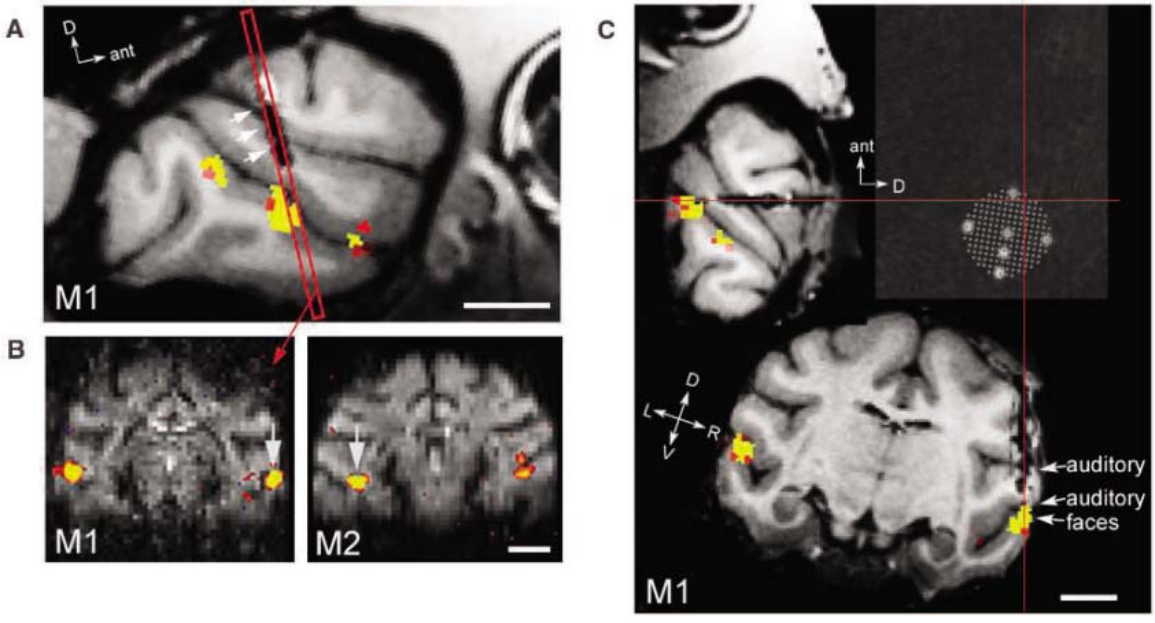

Fig. 1. Targeting an fMRI-identified face patch for single-unit recording. (**A**) A semisagittal section through the right hemisphere of monkey M1 showing three face-selective patches along the STS. Single-unit recordings in monkeys M1 and M2 were targeted to the middle face patch, located ~6 mm anterior to the interaural line; the red rectangle indicates a coronal slice passing through the middle face patch. The three white arrows point to the lesion left by the recording guide tube. (**B**) Two coronal slices showing the middle face patch in monkeys M1 (left) and M2 (right) (at A6.5 and A5.5, respectively). MION activation is overlaid on raw functional echo planar (EPI) images. Arrows point to the specific region targeted for electrophysiology in each monkey. In monkey M1, the targeted face patch was located on the lower lip of the STS in the right hemisphere. In monkey M2, the targeted face patch was located in the fundus of the STS in the left hemisphere. (**C**) Face patches and guide-tube track in three dimensions, rotated into the coordinate system of the recording grid (monkey M1). After chamber implantation, a high-resolution anatomical scan was obtained with six oil-filled markers positioned inside a grid in the recording chamber. We determined which grid hole to use by rotating the brain, together with registered face-selective fMRI activation, into the coordinate system defined by these markers. This panel shows three orthogonal slices passing through the point marked by the intersection of the red lines. Cells in this monkey were recorded from the hole at the intersection of the red lines, and from two adjacent, more-medial holes in the same row of the grid. The dark elongated lesion confirms that the guide tube passed through this point to accurately and precisely target the middle face patch. We recorded from all cells encountered between the start of the gray matter and the start of the white matter in the lower bank of the STS. Scale bar, 1 cm. $P < 10^{-4}$ for MION activations.

mean absolute magnitude of the FSI was 0.90 in monkey M1 and 0.87 in monkey M2, which correspond, respectively, to a 19:1 and a 14:1 ratio of face-to-nonface object response. In the single-unit literature, cells are typically classified as face selective if they respond at least twice as strongly to faces as to nonface objects (*16*, *17*). By this criterion, all but 8 out of 310 total visually responsive cells, or 97%, were face selective (we considered cells that were selectively inhibited by faces to be face selective as well; if we required an excitatory response to faces, then 280/310 = 90% of cells were face selective).

Because the monkeys were highly familiar with the 16 screening faces, one could hypothesize that exposure to these specific faces contributed to the cells' selectivity. This appears unlikely for two reasons. First, we found that the face selectivity of units in the middle face patch did not depend on the particular set of images tested. Although some cells responded best to only one or a few faces (Fig. 2A, left, cell 40), many cells were responsive to a wide variety of face images, including familiar and unfamiliar faces, human and macaque faces, and even cartoon faces (fig. S3). Cells maintained their face selectivity when tested with a wide variety of novel face and nonface images, including monkey headless bodies and body parts, as well as hundreds of natural images. Second, because each of the 96 images in the screening set was shown equally often, we do not believe that selectivity for one particular subset of images (faces) could emerge from repetitive passive viewing of the whole set of images.

What was the selectivity of units that did not give a clear response to any of the 96 screening stimuli? When we encountered such a unit, in most cases we documented the nonresponsiveness and then advanced the electrode in search of the next unit. However, in cases where we were recording from a pair of units simultaneously and only one was visually responsive, we tested a battery of additional face stimuli (*18*) on the nonresponsive unit as well. We found that out of 14 initially non–visually-responsive units tested in this way, 9 actually were responsive to face stimuli but were selective for nonfrontal views, different expressions, or monkey faces. None of the remaining five units showed a significant response to any nonface object. It is therefore likely that many, if not all, non–visually-responsive units were similarly selective for face characteristics not included in the set of screening stimuli.

The local field potential (LFP) represents summated excitatory and inhibitory synaptic potentials in thousands of neurons around the electrode tip. It has been reported that the LFP correlates better than single units with the fMRI signal (*19*). Evoked LFPs recorded from monkeys M1 and M2 are shown in fig. S4. In both monkeys, two large face-selective troughs with peak magnitudes at 130 ms and 200 ms were evident in the LFP. We observed these face-selective LFP troughs at almost all recording sites in the middle face patch, providing further evidence that population activity within this face patch was strongly face selective. The existence of two face-selective troughs suggests two discrete stages of face processing, possibly triggered by the arrival of feedforward and feedback/recurrent inputs, respectively.

One fundamental function of face processing is to identify individuals. Cells responding sparsely and robustly can be used not just to detect the presence of a face, but to discriminate the identity of a particular face. To measure how much information these face-selective cells carried about face identity (i.e., differences between different face images), we examined all cells for which the 96 faces and objects had been presented at least five times (94 cells). The response magnitude elicited by the 96 images in

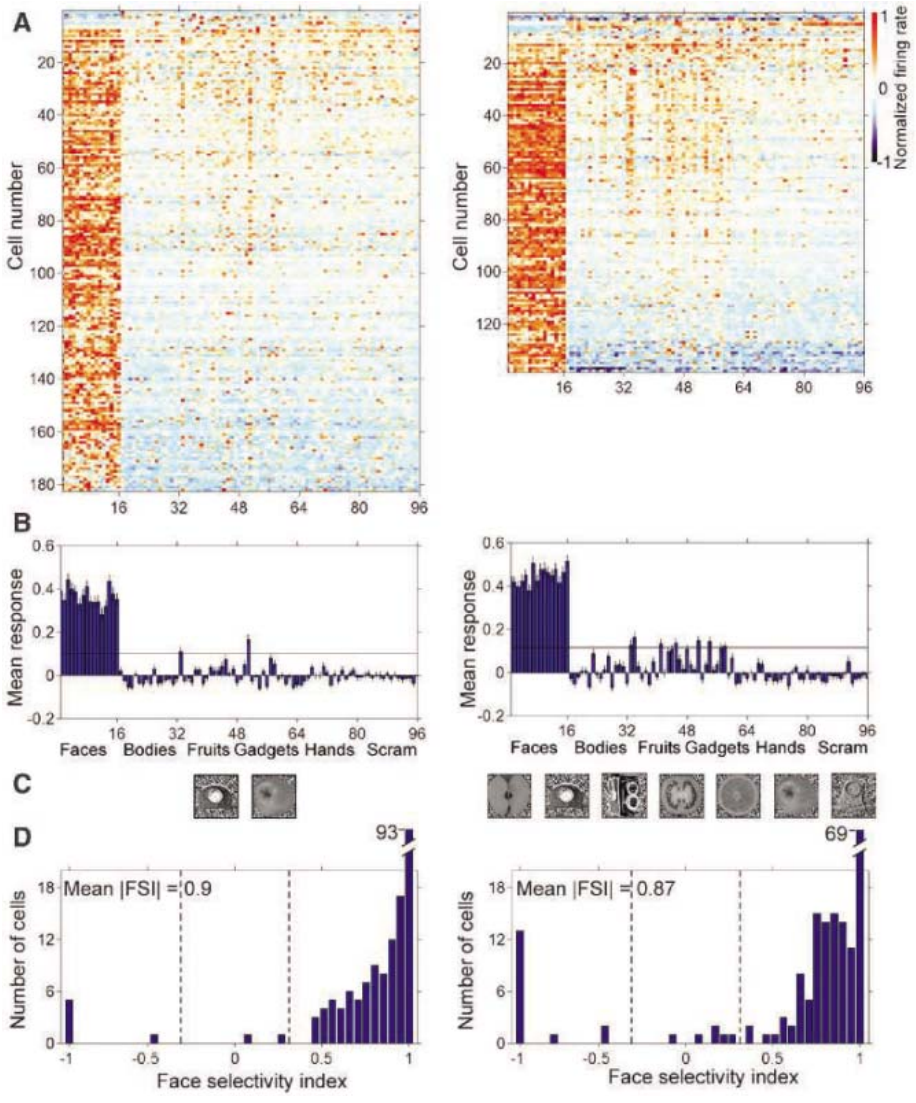

Fig. 2. Face selectivity of single units in the middle face patch. (**A**) Selectivity profiles of all visually responsive cells in monkeys M1 (left) (182 cells) and M2 (right) (138 cells) to 96 images of faces, bodies, fruits, gadgets, hands, and scrambled patterns (16 images per category, see fig. S1 for stimuli). Each row represents one cell and each column one image. The rows were sorted by the FSI, and the columns were sorted by image category. To compute selectivity profiles for each cell, responses to the 96 images were averaged over a 200-ms interval starting at the response latency, the baseline (the average response from 0 to 50 ms) was subtracted, and the response normalized. The average response time course to each of the 96 images is shown in fig. S6. (**B**) Average response to each of the 96 images across all visually responsive cells in monkeys M1 and M2. Error bars represent ±1 SE. The black line indicates six average SEs. (**C**) Nonface images that elicited a response above six average SEs in monkeys M1 and M2. Images are sorted from left to right by decreasing elicited response magnitude. (**D**) Distribution of FSIs across all visually responsive cells. Dotted lines indicate |FSI| = 0.33 (corresponding to a 2:1 ratio of face-to-nonface object response).

these 94 cells on four trials was averaged to yield, for each image, a population vector ("template vector"). We then asked whether we could predict the identity of an unknown image from the activity it elicited across the population of 94 cells on the remaining fifth trial ("test vector"). Identification was performed by determining the template vector to which the test vector was closest in Euclidean distance (Fig. 3A). If the population response correctly identified a particular image, then the 96 × 96 matrix of (test vector, template vector) distances should have a minimum value on the diagonal in the row corresponding to that image (chance = 1/96). We also examined categorization by using the following test: If the population response correctly categorized a particular image as belonging to one of the six stimulus categories, then the response to that image should be closest to the mean of the 16 template vectors in the same category (chance = 1/6).

Figure 3B shows the percent correct identification and categorization obtained using this algorithm. Mean individual face identification accuracy was 74%, and mean face categorization accuracy was 100%. Thus, information about face category and identity is available within this patch of cortex. Performance was significantly better for faces than for nonface objects, for both individual identification (t test, $P < 2 \times 10^{-16}$) and categorization (*t* test, $P < 5 \times 10^{-19}$).

Evidence from human psychophysics suggests that objects are identified at the category level (e.g., face versus fruit) before they are identified at the individual level (*20*). A physiological correlate of this is that information about face category precedes information about face identity by an average of 51 ms in face-selective cells recorded from the anterior STS (*21*, *22*). To examine the time course of identity and category information in single units in the middle face patch, we computed time-varying test and template vectors from average responses within a 50-ms sliding window. Categorization performance reached its maximum earlier (133 ms) than did identification performance (192 ms) (Fig. 3C).

Single units in the middle face patch of the macaque temporal lobe showed a remarkable specificity for face processing and contained a much higher concentration of face-selective cells than reported previously. Indeed, the only nonface images that elicited significant (albeit small) responses across the population were clocks and round fruits, which share a common shape attribute with faces. In agreement with previous single-unit studies of face-selective cells in the temporal lobe, cells in the middle face patch carried information about the identity of individual faces distributed across the population (*23*–*25*), and they showed a face-inversion effect (*17*, *26*). The responses of cells in the middle face patch clearly tended toward distributed coding within the domain of faces, because many cells were activated by a wide range of face stimuli, and a stimulus set containing only 16 faces elicited significant activation in 80% of all cells. The cells in this patch may be performing the "structural encoding stage" of face processing (*27*); at this stage, faces are analyzed in terms of structural properties and semantic identity has not yet been made explicit.

Several previous single-unit studies have described a scattered clustering of face-selective cells in the temporal lobe (*8*, *17*, *28*), suggesting an underlying architecture of clumps (*29*) or columns (*28*), although these clusters may be larger (0.5 to 2 mm) than classical columns found in early sensory areas (*7*, *30*). Furthermore, optical imaging studies have found ~1-mm spots in anterior inferotemporal cortex that are selective for faces (*31*). Large parts of the temporal lobe may indeed be tessellated by columns selective for different kinds of objects. However, because of its reproducible anterior-posterior location and selectivity properties (both single-unit and LFP) across animals and its relatively large size (~16 mm^2), the middle face patch appears to constitute a different level of functional organization: a discrete area dedicated to face processing.

Why is it important that the brain contains an area consisting entirely of face-selective cells? First, this indicates that the brain uses a specialized region to process faces. Second, no brain region has previously been identified that is selective for a single visual form; in this sense, the fMRI face patches are analogous to the widely studied area MT/V5, which is specialized for processing visual motion. Third, the finding that essentially all cells within this region were face-selective implies that either all the inputs are already face-selective, or a face-selective output can be generated from non– or partially face-selective inputs in just one step. Fourth, the fact that fMRI and single units were both specific for the same visual features confirms and extends previous evidence that the hemodynamic signal of fMRI can be highly correlated with single-unit activity, in higher order regions (*32*) as well as in lower tier regions (*33*). Fifth, the fact that many face-selective cells also showed a weak response to round clocks and fruits indicates that domain-specific face processing emerges at an early stage in form processing. And lastly, the grouping together of

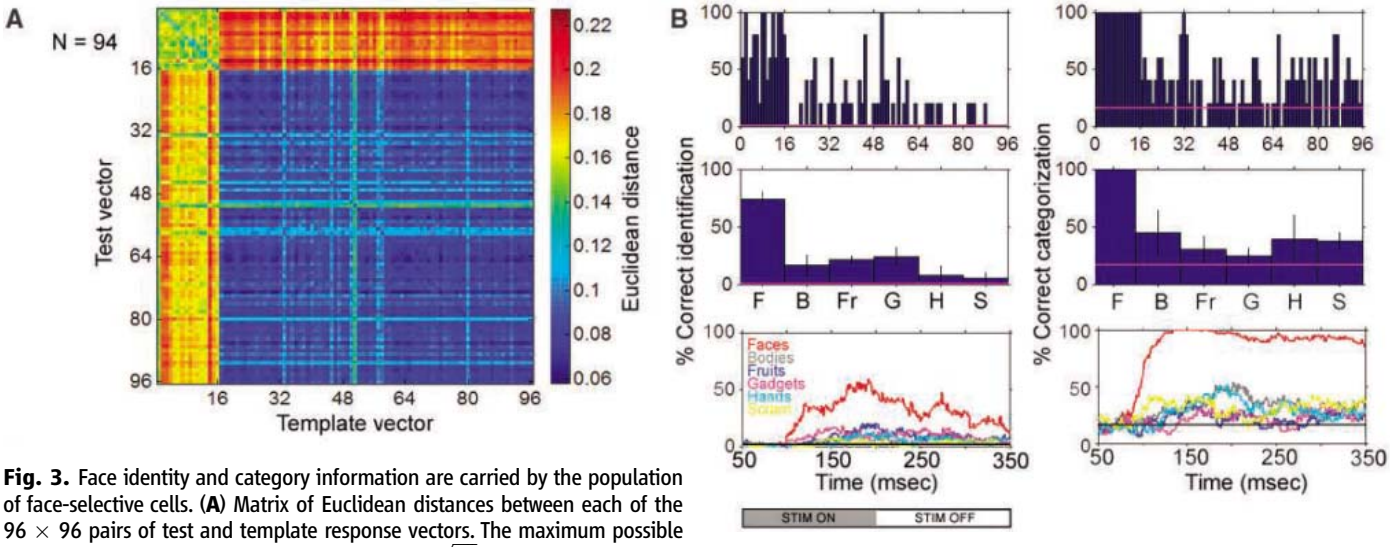

Fig. 3. Face identity and category information are carried by the population of face-selective cells. (**A**) Matrix of Euclidean distances between each of the 96 × 96 pairs of test and template response vectors. The maximum possible distance between a test and a template vector is $\sqrt{94}$. (**B**) The top row shows the percent correct identification and categorization for each image, based on a nearest neighbor algorithm. The middle row shows the same data grouped by category (F, faces; B, bodies; Fr, fruits; G, gadgets; H, hands; S, scrambled patterns). Error bars represent ±1 SE. The bottom graphs are the percentages of correct identification and categorization for six different categories as a function of time after stimulus presentation, computed using a 50-ms sliding window. Chance performance would be 1/96 for identification and 1/6 for categorization (indicated by the horizontal line in each graph). Data are from monkey M1.

so many face-selective cells reiterates the advantages of modular architecture: An area consisting entirely of face-selective cells could achieve the richness of interconnections between large numbers of face-selective cells necessary to support holistic face processing.

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14. A significant response was defined as a reproducible response greater than baseline by at least 1 SD of the baseline firing for 20 consecutive bins.
15. Figure S5 shows the response profiles of all visually responsive cells in each monkey, sorted by the grid hole from which the cells were recorded (three grid holes in monkey M1 and three grid holes in monkey M2). In monkey M1, all three grid holes were loaded with face-selective cells. Similarly, in monkey M2, in both of the densely sampled grid holes, almost all visually responsive cells were face selective. Thus we can confidently conclude that the center of the fMRI face patch consists almost entirely of face-selective cells, and moreover this central region is not confined to a single millimeter-sized column, but covers a region at least 2 to 3 mm wide.
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Supporting Online Material

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- **Prospects**
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  (*Hugh Brown* / Phil Attard / Kari Dalnoki-Veress / H. Hoelscher)
- **Adhesion in Living Systems**
  (*Wendy Thomas* / Jim Callow / Benny Geiger)
- **Novel Uses of Adhesion**
  (*Paul Foreman* / Al Crosby / Nancy Sottos)
- **Bio-Inspired Adhesion**
  (*John Wilker* / Phillip Messersmith / Chuck Frihart / E. Artz)
- **Applications**
  (*David Dillard* / R.D. Adams / Steve Bennison / Greg Schueneman)
- **Interfacial Adhesion**
  (*Anand Jagota* / Chris Stafford / Jay Feinberg)
- **Adhesion at Small Length Scales**
  (*C.Y. Hui* / Mark Robbins / Pierre Nassoy / Joelle Frechette)
- **Perspectives**
  (*Jeff Koberstein* / Etienne Barthel / Keith W. Waldron)

ANGIOTENSIN
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SEP 10-15, 2006
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KATHY GRIENDLING, VICE CHAIR

- **Transcriptional Effects of Angiotensin II**
  (*Allesandro Capponi* / Rajendra Tangirala / Levon M Khachigian / William Rainey)
- **Pleiotropic Effects of Angiotensin Receptors**
  (*Walter G. Thomas*)
- **The Renin Receptor**
  (*Thomas Unger* / Genevieve Nguyen / Jan Danser / Heiko Funke-Kaiser / Charles Schwartz)
- **Angiotensin Converting Enzyme: New Pathways and Functions**
  (*Kenneth E. Bernstein* / Gregory Shen / Junji Takeda / Nigel M. Hooper / Sebastien Fuchs / Ingrid Fleming)
- **Angiotensin II and Cerebrovascular Inflammation**
  (*Juan Saavedra* / Marta Ruiz-Ortega / Stephan Zorad / Julius Benicky)
- **Genomics, Genetics and Epigenetics**
  (*Yigal M. Pinto* / Eric Olson / Blanche Schroen)
- **Young Investigator Session**
  (*Kenneth M. Baker*)
- **A Functional Role for the Renin Angiotensin System in T Lymphocytes**
  (*Jon A. Weidanz* / Dominik Müller / Michael Aviram)
- **Angiotensin II and Oxidative Stress**
  (*Patrick J. Pagano*)
- **Late Breaking News in Angiotensin Research**
  (*Curt D. Sigmund*)

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  (Todd Martinez / Terry Miller / Michael Baer / Fleming Crim / J.C. Tully / S. Hammes-Shiffer / W. Domcke / L. Cederbaum / A. Wodtke)
- **Cold Molecules**
  (R. Miller / Andrei Vilesov / K.B. Whaley / J. Hutson)
- **Reaction Dynamics**
  (S.R. Leone / R. Kaiser / W. Miller / D. Truhlar / M. Lester / M. Okamura / M. Brouard / G. Hall / S. Klippenstein / S. Gable)
- **Photoelectron Probes of Dynamics**
  (Carl Lineberger / D. Neumark / M. Johnson / C. Ng / P. Johnson / F. Merkt / T. Gallagher / H. Fielding)
- **New Spectroscopies**
  (Alex Benderskii / C. Schmuttenmaer / M. Quack / Ara Apkarian / D. Blank)

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- **Pathology and Inflammation**
  (Tracy Brooks / David Miller / Eng Lo / Sarah Thomas)
- **Beyond the Barriers: Retinal-, Spinal-, Tumor Barriers; Extracellular Transport**
  (Nurit Kalderon / Joe Fenstermacher / Arparna Lakkaraju / Christoph Hartmann / Joan Abbott)
- **Selected Abstracts for Oral Presentation**
  (*Tom Davis*)

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  (*Lluis Mir* / Karl Schoenbach / Ephraim Tekle / Richard Nuccitelli / Rumy Dimova / Rafi Korenstein)
- **Electrical Detection of DNA**
  (*Hubert Girault* / Aleksei Mulchandani / Serge Cosnier / Chad Mirkin)
- **Exchange Across Biological Barriers VI: From Exocytosis to Patch Clamp**
  (Jens Rettig / Christian Amatore / Kate Klemic / Franscico Benazilla / Ian Parker)
- **Endogenous Electric Fields I: Sensitivity by Animals**
  (Christiane Timmel / Hendrik Mouritsen)
- **Endogenous Electric Fields II: Role in Wound Healing and Spinal Cord Regeneration**
  (*Raphael Lee* / Richard Borgens / Marie Filbin / Colin McCaig)
- **Hot Topics**
  (*Ann Rajnicek*)

BIOINTERFACE SCIENCE
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
OCT 22-27, 2006
ASHUTOSH CHILKOTI &
JEFFREY HUBBELL, CO-CHAIRS
MARCUS TEXTOR, VICE CHAIR

- **Engineering Designer Biomolecules**
  (*Andy Ellington* / Andreas Pluckthun / Kai Johnsson)
- **Precision Engineering of Surfaces**
  (*Paula Hammond* / Nick Abbott / Craig Hawker)
- **Engineering the Interface**
  (*Emmanuel Delamarche* / Phil Messersmith)
- **Quantifying and Visualizing the Bio-Interface**
  (*Juergen Plitzko* / Denis Wirtz / Paul Cremer)
- **Dynamic Biointerfaces**
  (*Milan Mrksich* / Viola Vogel)
- **Biomembranes on a Chip**
  (*Joydeep Lahiri* / Jay Groves / Fredrik Hook)
- **Nanostructured Surfaces in Biology**
  (*Joachim Spatz* / Linda Griffith)
- **Molecular Detection Schemes**
  (Niles Pierce / Annelise Barron / Chad Mirkin)
- **Biomolecular Detection at the Single Molecule Limit**
  (*Hagan Bayley*)

BIOLOGY OF 14-3-3 PROTEINS
THE QUEEN'S COLLEGE
OXFORD, UK
AUG 27-SEP 1, 2006
ALASTAIR AITKEN, CHAIR
TOHRU ICHIMURA, VICE CHAIR

- **Keynote Addresses**
  (John Scott / Tony Pawson)

- **Structure and Ligand Recognition**
- **Mitogenic and Oncogenic Signal Transduction**
- **Cell Cycle Control and Apoptosis**
- **Genetics and Development**
- **Metabolic Regulation**
- **Hot Topics: Novel Functions and Regulation**
- **14-3-3 and Brain Diseases**
- **14-3-3 in Receptor Signaling**

BIOMINERALIZATION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 30-AUG 4, 2006
JOANNA AIZENBERG, CHAIR
JAMES DE YOREO, VICE CHAIR

- **Mechanisms of Crystal Growth and Inhibition in Mineralized Tissues and In Vitro I: Physico-Chemical Perspective** (*Jim De Yoreo* / George Nancollas / Mike Ward)
- **Mechanisms of Crystal Growth and Inhibition in Mineralized Tissues and In Vitro II: Control of Calcium Carbonate Formation** (*Fiona Meldrum* / Lia Addadi / Helmut Cölfen / Nico Sommerdijk)
- **Selected Posters for Oral Presentation I**
- **Biosilicification Mechanisms** (*Carole Perry* / Manfred Sumper / Mark Hildebrand)
- **Cell/Matrix Regulation of Mineralization in Vertebrates** (*Irving Shapiro* / Teresa Nicolson / Yoshiro Takano / Willi Jahnen-Dechent / Mike Hubbard)
- **Biominerals and Prokaryotes** (*Dennis Bazylinski* / Michael Winklhofer / Rajesh Naik)
- **Biooptics and Biomechanics: Structure-Function Relations** (Pete Vukusic / Christine Ortiz / Paul Zaslansky)
- **Selected Posters for Oral Presentation II**
- **Tissue Engineering** (*Tom Webster* / Pam Yelick / Bill Landis)
- **Protein-Mineral Interactions** (*Marc McKee* / Frederic Marin / Candan Tamerler-Behar / Melinda Duer)
- **Plenary Lecture** (*Joanna Aizenberg* / Sam Stupp)

BIOORGANIC CHEMISTRY
MAGDALEN COLLEGE
OXFORD, UK
JUL 30-AUG 4, 2006
LESLIE SLOAN & PETER TONGE, CO-CHAIRS
JESSICA FRIEDMAN &
BLAKE PETERSON, CO-VICE CHAIRS

- **Antibiotics: Biosynthesis and Mechanisms of Action** (Jim Naismith / Wilfred van der Donk / Suzanne Walker)
- **Evolution and Design** (Andreas Plückthun / Alanna Schepartz / Mark Smythe / Hiro-Aki Suga)
- **Enzyme Catalysis and Inhibition** (John Blanchard / Martin Tanner / Neil Thomas)
- **Following the Yellow Brick Road: Pathways for Assembling Molecules in Cells** (Tadhg Begley / Michael Burkart / Rajesh Gokhale)
- **Drug Discovery** (Girija Krishnamurthy / David Rees / Paul Richardson)
- **Understanding and Dissecting Complex Systems** (Shankar Balasubramanian / Hagan Bayley / Dan Kahne / Jürgen Plitzko)
- **Diversity: The Spice of Life** (Sharon Cload / Peter Seeberger / Derek Tan)
- **Signal Transduction and Gene Expression** (Karen Anderson / Phil Cole / Mary Kay Pflum)
- **Chemical Biology of Diseases** (Chris Dobson / Gary Glick / Chris Schofield)

BIOPOLYMERS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 11-16, 2006
DAVID LYNN & SARAH WOODSON, CO-CHAIRS
GEORGE MAKHATADZE, VICE CHAIR

- **Self-Assembly of Large Cellular Complexes** (*Jamie Williamson* / Bryan Krantz / Robert Liddington / Fadel Samatey)
- **Ligand Recognition and Protein Folding** (Lila Gierasch / Michael Hecht / Rama Ranganathan)
- **Protein Amyloids** (*Jeff Kelly* / Glenn Millhauser / Robert Tycko / Rajaraman Krishnan (Lindquist Lab))
- **Membrane Proteins** (*Stephen White* / Karen Fleming / Sergei Sukharev)
- **RNA Folding and Dynamics** (*Martha Fedor* / Taekijp Ha / Lois Pollack)
- **Switches and Sensors** (Andy Ellington / Justin Gallivan / Marc Ostermeier)
- **Biomolecules as Nanomaterials** (Paula Hammond / Chengde Mao / Milan Stojanovic / Samuel Stupp)
- **Late Breaking News Selected from Poster Abstracts**

BRAIN ENERGY METABOLISM & BLOOD FLOW
MAGDALEN COLLEGE
OXFORD, UK
AUG 20-25, 2006
MARTIN LAURITZEN, CHAIR
EDITH HAMEL, VICE CHAIR

- **Keynote Lecture** (*Martin Lauritzen* / Wolf Singer)
- **Energy Metabolism and Budgeting** (*Nicola R. Sibson* / Maria Erecinska / David Attwell)
- **Energetic Costs of Neurotransmission During Activation** (*Margaret Wong-Riley* / Kevin Behar / Pierre Magistretti / Albert Gjedde)
- **Imaging Signals Evoked by Spontaneous Cortical Activity** (*Gyorgy Buzsaki* / Amos Arieli / Marcus E. Raichle)
- **Neurovascular Coupling in Vivo** (*Ute Lindauer* / John Mayhew / Anna Devor / Costantino Iadecola)
- **Neurovascular Coupling in Vitro** (*Brian MacVicar* / Eric A. Newman / Bruno Cauli)
- **Methodological Frontiers I** (*Arthur Toga* / Amiram Grinvald / David Boas / Karl A. Kasischke)
- **Methodological Frontiers II** (*Peter van Zilj* / Afonso C. Silva / Richard Buxton)
- **Clinical Aspects of Neurovascular and Metabolic Coupling** (*Anthony Strong* / Astrid Nehlig / John Pickard / Jens Dreier)
- **Hot Chair Session** (*Joel Greenberg*)

CANCER MODELS & MECHANISMS
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 30-AUG 4, 2006
RENE BERNARDS, CHAIR
WILLIAM KAELIN, VICE CHAIR

- **Keynote Lecture** (Pier Paolo Pandolfi)
- **Self Sufficiency in Growth Signals** (*Terry van Dyke* / Anton Berns)
- **Insensitivity of Anti-Growth Signals** (*Lewis Chodosh* / Xiao-Fan Wang)
- **Tissue Invasion and Metastasis** (*Joan Massague* / Harold Moses / Bill Kaelin)
- **Limitless Replicative Potential** (*Bill Hahn* / Jerry Shay / Ron DePinho)
- **Sustained Angiogenesis** (*Peter Carmeliet* / Napoleone Ferrara / Laura Benjamin)
- **Evading Apoptosis** (*Gerard Evan* / Karen Vousden)
- **Epigenetic Control and Genomic Instability** (*Ashok Ventikaraman* / Dave Allis / Riccardo Fodde)
- **Functional Genetic Approaches to Cancer** (*Reuven Agami* / Steve Elledge / Julian Downward)
- **Predictive and Prognostic Biomarkers of Cancer** (*Louis Staudt* / Laura Van't Veer / Todd Golub)

CARDIAC REGULATORY MECHANISMS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 16-21, 2006
KENNETH PHILIPSON, CHAIR
DAVID EISNER &
JONATHAN LEDERER, CO-VICE CHAIRS

- **Ca^{2+} Regulatory Proteins** (*Larry Jones* / Kurt Beam / Wayne Chen / Sandor Gyorke)
- **Ca^{2+} in Contractility** (*Martin Morad* / Mark Cannell / Shey-Shing Sheu / Andy Trafford / Clive Orchard)
- **Signaling** (*Joan Heller Brown* / Jeff Molkentin / Litsa Kranias / Yibin Wang)
- **Channels, Transporters, and Function** (*Ed Lakatta* / Don Hilgemann / Jerry Lingrel / Richard Vaughan-Jones / Mark Anderson / Xander Wehrens)
- **Rhythms and Arrhythmias** (*Jim Weiss* / Jeff Saffitz / Colleen Clancy / Kevin Donahue)

- **Stress, Strain, and Microdomains**
  (*Susan Steinberg* / Ed Moore / Peter Mohler / John Solaro / Meredith Bond / Elizabeth McNally)
- **Pathophysiology of EC Coupling**
  (*David Eisner* / Don Bers / Barbara Casadei / Elizabeth Murphy)
- **Death, Failure, Recovery, Repair**
  (*Jon Lederer* / Jeff Robbins / Steve Houser / Loren Field / Eduardo Marban / Christine Seidman)
- **Keynote Speaker**
  (Andrew McCulloch)

CATALYSIS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 25-30, 2006
ROBERT DAVIS, CHAIR
STUART SOLED, VICE CHAIR

- **Keynote Lectures**
  (Avelino Corma / D. Wayne Goodman)
- **Catalysis Fundamentals**
  (Jochen Lauterbach / Matthew Neurock / Rutger van Santen / Bert Weckhuysen)
- **Biocatalysis, Biorenewables and Fuel Cells**
  (Fraser Armstrong / Shimshon Gottesfeld / Todd Werpy)
- **Catalytic Conversion of Hydrocarbons**
  (Johannes Lercher / Susannah Scott / Peter Stair)
- **Novel Catalytic Materials**
  (Christopher Jones / Alexander Katz / Karl Strohmaier)

CELL BIOLOGY OF THE NEURON
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 18-23, 2006
CRAIG GARNER & YUKIKO GODA, CO-CHAIRS
ANN MARIE CRAIG &
JOSHUA KAPLAN, CO-VICE CHAIRS

- **Keynote Lecture**
  (Josh Sanes)
- **Cell Migration, Axo-Dendritic Growth and Patterning**
  (Mike Ehlers / Shelley Halpain / James Jontes / Stephen Strittmatter / Linda Van Aelst)
- **Synapse Organization and Assembly**
  (Vivian Budnik / Anne Marie Craig / Anirvan Ghosh / Yishi Jin / Noam Ziv)
- **Presynaptic Membrane Traffic**
  (Ed Chapman / Pietro De Camilli / Erwin Neher / Janet Richmond / Tim Ryan)
- **Postsynaptic Receptor Dynamics**
  (Rick Huganir / Josh Kaplan / Elly Nedivi / Antoine Triller)
- **Synapse Scaling and Plasticity**
  (Graeme Davis / Bai Lu / Gina Turrigiano)
- **Signaling Mechanisms Underlying Network Activity**
  (Cori Bargmann / Dan Johnston / Richard Tsien)

CELL DEATH
BIG SKY RESORT
BIG SKY, MT
SEP 10-15, 2006
J. MARIE HARDWICK, CHAIR
GUY SALVESEN, VICE CHAIR

- **Cell Death Perspectives and New Insights**
  (*Doug Green* / Sally Kornbluth / David Vaux)
- **Mitochondria Structure and Function**
  (*Richard Youle* / David Nicholls / Ian Dawes / Liz Jonas)
- **Death-Survival Conflicts in the Nervous System**
  (*Pierluigi Nicotera* / Len Kaczmarek / Zheng Li)
- **Non-Apoptotic Pathways**
  (*Craig Thompson* / Eric Baehrecke / Richard Flavell / Fedor Severin)
- **Molecular Mechanisms of Cell Death**
  (*Junying Yuan* / Kristin White / Emily Cheng)
- **New Pathways and Therapeutic Targets**
  (*Vishva Dixit* / Jürg Tschopp / Don Nicholson / Chris Akey)
- **Cell Death Mechanisms in Cancer and Aging**
  (*Jean Wang* / Karen Vousden / Nigel Waterhouse / Valter Longo)
- **Cell Death in Disease Pathogenesis**
  (*Eileen White* / Tak Mak / Yoshihide Tsujimoto / Richard Kolesnick)
- **Talks Selected from Abstracts, Poster Sessions and Keynote**
  (*Michael Hengartner*)

CELLULAR & MOLECULAR FUNGAL BIOLOGY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUN 18-23, 2006
AARON MITCHELL &
ANNE OSBOURN, CO-CHAIRS
NEIL GOW & NANCY KELLER, CO-VICE CHAIRS

- **Epigenetic States**
  (*Brendan Cormack* / Shiv Grewal / Richard Bennett / Mick Tuite)
- **Development and Cell Biology**
  (*Judy Berman* / Gero Steinberg / Michelle Momany / Fred Chang / Nick Read)
- **New RNA Functions**
  (*Michael Feldbrügge* / Ralf-Peter Jansen / Alexander Hüttenhofer / Ambro Van Hoof)
- **Genomes and Evolution**
  (*Geraldine Butler* / Gillian Turgeon / Daniela Delneri / Fred Dietrich / Joe Heitman)
- **Small Molecules**
  (*Dominique Sanglard* / Thomas Edlind / David Perlin / Cameron Douglas)
- **Primary and Secondary Metabolism**
  (*Nancy Keller* / Bill Nierman / Pietro Spanu / Frances Trail / Barry Scott)
- **Population Structure and Ecology**
  (*John Taylor* / Liz Turner / Jeff Townsend / Matthew Fisher)
- **Cell Surfaces, Adhesion and Invasion**
  (*Barbara Valent* / Gerry Fink / Regine Kahmann / Anita Sil / Tamara Doering)
- **Late Breaking Topics**

CERAMICS, SOLID STATE STUDIES IN
PROCTOR ACADEMY
ANDOVER, NH
AUG 13-18, 2006
JOHN BLENDELL, CHAIR
ROBERT COOK, VICE CHAIR

- **Modeling and Simulation of Grain Growth**
  (*Catherine Bishop* / James Warren / Veena Tikare)
- **Computational Design of Microstructure**
  (*W. Craig Carter* / David Wu / R. Edwin García)
- **Microstructure Development**
  (*Randy Hay* / Rowland Cannon)
- **Brief Poster Presentations**
  (*Robert Cook*)
- **Grain Growth Control in Bulk Materials**
  (*Helen Chan* / Susan Trolier-McKinstry / Suk-Joong Kang / Martin Harmer)
- **Interfaces and Grain Boundaries**
  (*Susan Sinnott* / Z.L. Wang / I-Wei Chen)
- **Thin Films**
  (*Kevin Ewsuk* / Glen Fox / Marcel Rost / Paul Salvador)
- **Characteristics of Microstructure**
  (*Greg Rohrer* / Pat Patterson / Brent Adams)
- **Fuel Cells**
  (*John Halloran* / Jûrgen Fleig / Katsuyo Thornton)

CHEMOTACTIC CYTOKINES
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
SEP 17-22, 2006
SERGIO LIRA, CHAIR
AMANDA PROUDFOOT, VICE CHAIR

- **Keynote Lecture**
  (*Ron Germain*)
- **Chemokines in Development**
  (*M. Lipp* / A. Raz / D. Littman / A. Mantovani)
- **Chemokine Drugs**
  (T. Wells / R. Horuk / J. Moore)
- **Chemokines in Homeostasis I**
  (*S. Kunkel* / A. Luster / B. Moser / A. Proudfoot / A. Alcami / C. Martinez-A)
- **Chemokines in Homeostasis II**
  (*M. Thelen* / L. Glimcher / R. Forster / A. Rot / H. Rosen)
- **Chemokines in Disease I**
  (*I. Charo* / R. Ransohoff / G. Diaz / K. Matsushima / J. Bromberg / W. Hancock)
- **Chemokines in Disease II**
  (*A. Zlotnik* / P. Murphy / B. Rollins / R. Strieter)
- **Imaging/Trafficking**
  (*M. Dustin* / J. Cyster / M. Cahalan / H.C. Reinecker)
- **Late Breaking Topics / Frontiers**

COMBINATORIAL CHEMISTRY
THE QUEEN'S COLLEGE
OXFORD, UK
AUG 20-25, 2006
R. KIP GUY, CHAIR
DARYL SAUER, VICE CHAIR

- **The State of Combichem**
  (*R. Kip Guy* / Charles Craik / Anthony Czarnik)
- **How Do We Design a Library?**
  (*Tudor Oprea* / Herbert Waldman / Andrew Leach / John Irwin)

- **Just What is a Validated Hit?**
  (*Stephen Frye* / Edgar Jacoby)
- **Academic Case Studies**
  (*Morten Grotli* / Morten Medal / Stefan Brase / Nina Kahn)
- **The NIH Roadmap**
  (*John Schwab* / Chris Austin / Jim Inglese / Donna Huryn / Steve Bryant)
- **Case Studies 1**
  (*Anthony Czarnik* / Steve Djuric / Christine Brotherton-Pleiss / Richard Lee)
- **New Technologies**
  (*Daryl Sauer* / Peter Seeburger)
- **Case Studies 2**
  (*Christine Brotherton-Pleiss* / Stephen Frye / Peter Grootenhuis / Sarathy Kesavan)
- **Chemical Biology**
  (*Nina Kahn* / Tudor Oprea / Morten Grotli / Andrea Cochran)

COMPUTATIONAL ASPECTS - BIOMOLECULAR NMR
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
SEP 24-29, 2006
MARTIN BLACKLEDGE, CHAIR
RAFAEL BRUSCHWEILER, VICE CHAIR

- **Perspectives on NMR in Structural Biology**
  (James Prestegard / Hartmut Oschkinat / Guy Montelione)
- **Data Acquisition and Spectral Processing**
  (*Bernhard Brutscher* / Eriks Kupce / Dominique Marion)
- **Interpreting Chemical Shifts for Protein Structure and Dynamics**
  (David Case)
- **Solid State NMR of Proteins**
  (*Anja Böckmann* / Rob Tycko / Lyndon Emsley / Ann McDermott)
- **Emerging Methods for Protein Structure Determination**
  (*Michael Nilges* / Michele Vendruscolo / G. Marius Clore / Markus Zweckstetter / Miguel Llinas)
- **NMR Studies of Kinetics, Dynamics and Interactions in Larger and more Complex Systems**
  (Carol Beth Post / Lewis Kay / Kathleen Hall)
- **NMR of Partially Folded and Unfolded Proteins**
  (*Harald Schwalbe* / Alan Fersht / Peter Wright / Tobin Sosnick / Stephan Grzesiek)
- **Domain Dynamics by NMR**
  (*Rafael Brüschweiler* / Claudio Luchinat / Nico Tjandra / David Fushman)
- **Dynamic Modes in Proteins**
  (*Martin Blackledge* / Geoffrey Bodenhausen / Arthur Palmer / Christian Griesinger / Dorothee Kern)
- **Macromolecular Complexes Using NMR and Complementary Techniques**
  (Alexandre Bonvin / Dmitri Svergun)
- **Alignment and Anisotropy**
  (Ad Bax)

COMPUTATIONAL CHEMISTRY
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
OCT 8-13, 2006
WILFRED VAN GUNSTEREN, CHAIR
JED PITERA, VICE CHAIR

- **Force Fields, Polarization**
  (*Wilfred F. van Gunsteren* / Alexander D. MacKerrell / Jay W. Ponder)
- **Quantum Methods, Quantum Dynamics**
  (*Walter Thiel* / Richard A. Friesner / Jürg Hutter / Dirk Bakowies / Irene Burghardt)
- **Reactions**
  (*Adrian Mulholland* / Arieh Warshel / Bernhard H. Schlegel)
- **Searching, Electrostatics, Free Energy**
  (*Philippe H. Hünenberger* / Mark Tuckerman / Gerhard Hummer / Johan Aqvist)
- **Drug Design, Docking**
  (*Peter W. Kenny* / Andrew Leach / Mark Murcko)
- **Biomolecular Modeling**
  (*Alan E. Mark* / Liu Haiyan / Bernard R. Brooks / Ken A. Dill)
- **Coarse-Graining**
  (*Florian Müller-Plathe* / Julian C. Shillcock / Siewert-Jan Marrink)
- **Applications, Membranes, History**
  (*David Beveridge* / *Bill Swope* / Paul Tavan / Benoit Roux / Olle Edholm / Herman J.C. Berendsen)

CORRELATED ELECTRON SYSTEMS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 18-23, 2006
J.C. SEAMUS DAVIS &
STEVEN GIRVIN, CO-CHAIRS
LEON BALENTS &
LOUIS TAILLEFER, CO-VICE CHAIRS

- **Spin Hall Effect, Spin Drag and Spin Accumulation**
  (*Allan MacDonald* / Charles Kane / Giovanni Vignale / Joe Orenstein / David Awschalom)
- **Advances in the Physics of 2DEG's**
  (*Catherine Kallin* / James Eisenstein / Vladimir Goldman / Smitha Vishveshwara / Horst Stormer)
- **Novel Quantum Phases and Phase Transitions**
  (*Sudip Chakravarty* / Chetan Nayak / M.P.A. Fisher / Leon Balents / Karyn Le Hur)
- **Correlated Electron Systems: Oxides**
  (*A. Mackenzie* / Norman Manella / G.-H. Gweon / Santiago Grigera)
- **Helium/Hydrogen Supersolids**
  (*William Brinkman* / Jason Ho / Moses Chan / Marcus Greiner)
- **Ultracold Trapped Fermions**
  (*Kathy Levin* / Debbie Jin / Randy Hulet / Chen Chin / W. Ketterle)
- **Graphene Physics**

CORROSION - AQUEOUS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 16-21, 2006
PHILIPPE MARCUS, CHAIR
ALISON DAVENPORT, VICE CHAIR

- **Passivity, Passivity Breakdown and Localized Corrosion**
  (*Shinji Fujimoto* / Kemal Nisancioglu / Jerry Frankel / Andrej Atrens / En-Hou Han)
- **Nanocorrosion**
  (*Vincent Maurice* / Ismael Diez-Perez / Patrik Schmuki)
- **Metal-Oxide-Polymer Interfaces, Coatings and Corrosion Inhibition**
  (*Digby Macdonald* / Martin Stratmann / Herman Terryn / Tooru Tsuru)
- **Biomolecules and Biofilms on Surfaces: Impact on the Corrosion Resistance**
  (Sachiko Hiromoto / Alain Bergel)
- **Environmental Issues of Metal Corrosion**
  (*Tim Burstein* / Inger Odnevall Wallinder)
- **Simulation, Modeling and Life Prediction**
  (*Roger Newman* / Jonah Erlebacher / John Scully)
- **Advances in Analytical and Electrochemical Methods for Corrosion Research**
  (*Nancy Missert* / Hugh Isaacs / Roland Oltra)
- **Corrosion Issues in Enabling Technologies**
  (*Mike Graham* / Yair Ein-Eli)

CYCLIC NUCLEOTIDE PHOSPHODIESTERASES
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 4-9, 2006
RICK COTE &
MARIE-JOSEPHE LEROY, CO-CHAIRS
FRANK MENNITI &
NIGEL PYNE, CO-VICE CHAIRS

- **The Expanding Family of PDEs: Novel PDEs in Lower Organisms**
  (*Joe Beavo* / Kenji Omori / Thomas Seebeck / Peter van Haastert / Shireen Davies)
- **Membrane Anchoring Proteins and Compartmentation of PDE**
  (*Lawrence Brunton* / John Scott / Rodolphe Fischmeister / Manuella Zaccolo / George Baillie / Donald Maurice)
- **Fundamentals of PDE Therapeutics: Structure of the Active Site and Drug Discovery**
  (Hengming Ke / Jayvardhan Pandit / Claire Lugnier / Sharron Francis)
- **Transcriptional and Translational Control of PDE Expression**
  (*Vincent Manganiello* / Chen Yan / Visvanathan Ramamurthy / Adam Lerner / Wito Richter)
- **PDEs in the Central Nervous System**
  (*James O'Donnell* / *Frank Menniti* / Han-Ting Zhang / Christopher Schmidt / Anthony West / Katerina Akassoglou)
- **Involvement of PDEs in Cellular Physiology**
  (*Miles Houslay* / Dermot Cooper / Eva Degerman / Robin Kleiman / Nigel Pyne)
- **PDE Function in the Cardiovascular System**
  (Andrew Marks / David Kass / Kimberly Dodge-Kafka / Matthew Movsesian)

- **PDE Inhibitor Therapy and Immune System Function**
  (*Marco Conti* / Celine Mehats / Kjetil Tasken / Catherine Jin / Patricia Podolin / Marc Gavin / Andrew Bender / Yan Tang)
- **Allosteric Regulation of the PDE Holoenzyme**
  (Nikolai Artemyev / Theodore Wensel / Joachim Schultz / Jackie Corbin / Arnold Ruoho)

DEFECTS IN SEMICONDUCTORS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 2-7, 2006
WLADEK WALUKIEWICZ, CHAIR
MATT MCCLUSKEY, VICE CHAIR

- **Hydrogen in Dilute Nitrides**
  (*Chris Van de Walle* / Michael Stavola / Sukit Limpijumnoong)
- **Nanostructures**
  (Phil Collins / Su-Hua Wei)
- **Photovoltaics**
  (*Eicke Weber* / Susanne Siebentritt / Mao-Hua Du)
- **Group III-Nitrides**
  (*Tim Veal* / Joel Ager / Achim Trampert)
- **Spintronic Materials**
  (*Oscar Dubon* / Paul Koenraad)
- **Wide Band Gap Semiconductors**
  (Paul Klein / Edward Lavrov / Slade Jokela)
- **Compound Semiconductors**
  (*Eugene Haller* / Anant Ramdas)
- **Silicon and Diamond**
  (*Patricia Mooney* / Anna Cavallini)

DIFFRACTION METHODS IN STRUCTURAL BIOLOGY
BATES COLLEGE
LEWISTON, ME
JUL 16-21, 2006
PAUL ADAMS, CHAIR
ELSPETH GARMAN, VICE CHAIR

- **Membrane Proteins and Complexes**
  (*Randy Read* / Jamie Cate)
- **X-Ray Data Collection and Processing**
  (*Nicholas Sauter* / Raimond Ravelli / Olof Svensson / Ana Gonzalez / Zbyszek Otwinowski)
- **Complementary Biophysical Methods**
  (*Elspeth Garman* / Laurence Barron / Hiro Tsuruta / Jim McDonnell)
- **Computational Methods**
  (*Ralf Grosse-Kunstleve* / Airlie McCoy / Thomas Schneider)
- **Electron Microscopy, Electron Diffraction and Neutron Diffraction**
  (*Bill Massover* / Wah Chui / Ken Downing / Paul Langan)
- **Difficult Structures and Challenging Problems**
  (Jennifer Doudna / Olga Mayans / Gloria Borgstahl)
- **Advances in Structure Refinement**
  (*Eleanor Dodson* / Gerard Bricogne / Garib Murshudov)
- **Structure Completion**
  (*Jane Richardson* / Tom Terwilliger / Tassos Perrakis)
- **New Imaging Methods**
  (*Andrew Leslie* / Chris Jacobsen)

DRINKING WATER DISINFECTION BY-PRODUCTS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
AUG 13-18, 2006
SUSAN RICHARDSON &
MARK NIEUWENHUIJSEN, CO-CHAIRS
BEN BLOUNT, VICE CHAIR

- **Drinking Water Treatment and DBP Formation - Part I**
  (*Fritz Frimmel* / Howard Weinberg / Stuart Krasner)
- **Drinking Water Treatment and DBP Formation - Part II**
  (*David Reckhow* / Phil Singer / Bill Mitch / Marco Vincenti)
- **New Toxicology Studies - Part I**
  (*Rex Pegram* / Jane Ellen Simmons / Michael Plewa)
- **New Toxicology Studies - Part II**
  (*Sid Hunter* / Tony DeAngelo / Ron Melnick / Richard Winn)
- **New Reproductive/Developmental Epidemiology Studies - Part I**
  (*Tye Arbuckle* / Mark Nieuwenhuijsen / David Savitz)
- **New Reproductive/Developmental Epidemiology Studies - Part II**
  (Claire Infante-Rivard / Sylvaine Cordier / Gabriella Aggazzotti)
- **Cancer Epidemiology**
  (*Jouni Jaakkola* / Ken Cantor / Manolis Kogevinas)
- **New DBP Exposure Studies**
  (*Jay Nuckols* / Ben Blount / Cliff Weisel / John Reif)
- **Integrating Occurrence and Formation, Exposure, Toxicity, and Epidemiology**
  (*Pauline Mendola* / Mark Nieuwenhuijsen / Susan Richardson / Stuart Krasner / Ben Blount / Ken Cantor / Ron Melnick / Steve Via)

DRUG CARRIERS IN MEDICINE & BIOLOGY
BIG SKY RESORT
BIG SKY, MT
AUG 20-25, 2006
THOMAS KISSEL &
ALEXANDER V KABANOV, CO-CHAIRS
KYUNG-DALL LEE &
DAVID SCHEINBERG, CO-VICE CHAIRS

- **Keynote Lectures**
  (Judah Folkman / David Tirell)
- **Nano-Engineered Delivery of Drugs and Genes**
  (Pat Stayton / Alexander Kabanov / Robert Prud'homme / Rainer Haag)
- **Gene Delivery**
  (Ernst Wagner / Vladimir Torchilin)
- **siRNA Delivery**
  (Judy Lieberman / Kunyuan Cui / Mano Manoharan / Martyn Davies)
- **Nanoscience and Medicine**
  (James R. Heath / Patrick Couvreur)
- **Antibodies and Drug Delivery**
  (Peter Senter / James D. Marks / Jan E. Schnitzer / William Banks)
- **New Developments in Drug Delivery**
  (Ronit Satchi-Fainaro / Dong Wang / Theresa Reineke / David Putnam / Suzie Pun / Christine Allen)
- **Drug Targeting**
  (Phil Low / Kit S. Lam / Chuck Grissom / Phil Thorpe)
- **Drug Carriers**
  (Wim Hennink / Frank Szoka)

DRUG METABOLISM
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 9-14, 2006
LESLIE BENET, CHAIR
JAE LEE, VICE CHAIR

- **Keynote Lecture**
  (Dennis Smith)
- **Pharmacogenomics**
  (*Kathleen Giacomini* / Mary Relling / David Flockhart / Walter Miller)
- **Probe Substrates**
  (*Kenneth Thummel* / Grant Wilkinson / Evan Kharasch / Kenneth Korzekwa)
- **In Silico/In Vitro/In Vivo Approaches**
  (*R. Scott Obach* / Michael Mayersohn / Karen Rowland-Yeo / Gabriele Cruciani / Franco Lombardo)
- **Animals-on-a-Chip**
  (*Michael Shuler* / Gregory Baxter / Shuichi Takayama)
- **Transporters (but not P-gp and MRP2) in the Intestine and Liver**
  (*James Polli* / Hiroyuki Kusuhara / Patrick Sinko / Alex Sparreboom)
- **Grad Student/Post Doc Selected Abstracts Oral Presentations**
  (*Henry Strobel*)
- **Metabolic Liabilities and Risk Assessment**
  (*Mark Grillo* / Amit Kalgutkar / Christine Dieckhaus / Christian Skonberg / Jeffrey Waring)
- **Regulation**
  (*Wen Xie* / Masahiko Negishi / Melissa Runge-Morris)

ELECTRODEPOSITION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 30-AUG 4, 2006
JAY SWITZER, CHAIR
THOMAS MOFFAT, VICE CHAIR

- **Opening Session: Organic Monolayers and Molecular Electronics**
  (*Tom Mallouk* / Dieter Kolb / Kohei Uosaki)
- **Nucleation and Growth**
  (*Dieter Kolb* / Peter Searson / Gery Stafford / Walther Schwarzacher)
- **Epitaxial Electrodeposition**
  (*Stanko Brankovic* / Olaf Magnussen / John Stickney)
- **Shape Control**
  (*Dan Schwartz* / Christine Orme / Kyoung-Shin Choi / Shuji Nakanishi)
- **Magnetic Materials**
  (*Philippe Allongue* / Giovanni Zangari / Karen Kavanaugh)
- **Nanotubes and Nanowires**
  (*Yasuhiro Fukunaka* / Tom Mallouk / Patrik Schmuki / Reg Penner)
- **Recent News: Poster Summaries and Short Talks**
  (*Tom Moffat*)
- **Nanocrystals and Nanocomposites**
  (*Jan Fransaer* / Gary Hodes / Takayuki Homma / Jan Talbot)
- **Electrodeposition for Microelectronics**
  (*Jon Reid* / Lili Deligianni / Alan West)

ELECTRON DONOR ACCEPTOR INTERACTIONS
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 13-18, 2006
CLIFFORD KUBIAK &
MATTHEW ZIMMT, CO-CHAIRS
MALCOLM FORBES &
LEIF HAMMARSTROM, CO-VICE CHAIRS

- **Biological Electron Transfer**
  (*Ana Moore* / Robert Cave / Brian Crane / Melvin Okamura / Jay Winkler)
- **Cruickshank Symposium**
  (*Marshall Newton* / Noel Hush / Mark Ratner)
- **Designed Interfaces**
  (*Malcolm Forbes* / Maria Rampi / David Waldeck)
- **Frontiers of Donor-Acceptor Interactions**
  (*Cliff Kubiak* / Dirk Guldi / Frederick Lewis / Rajendra Rathore)
- **Interface Spectroscopy and Dynamics**
  (*Matthew Zimmt* / Tim Lian / Kohei Uosaki / Xiaoyang Zhu)
- **In Vivo Electron Transfer**
  (*Leif Hammarstrom* / Holger Dau / Derek Lovely / William Woodruff)
- **Materials and Devices**
  (Louis Brus / Robert Dickson / Alessandro Troisi)
- **Single Molecule Studies**
  (*Michael Wasielewski* / Amy Blum / H. Peter Lu / Paul McEuen / Nongjian Tao)
- **Ultrafast Dynamics**
  (*Vladimiro Mujica* / Dmitry Matyushov / John Papanikolas / Jeffrey Zink)

ELECTRONIC PROCESSES IN ORGANIC MATERIALS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 30-AUG 4, 2006
PAUL BARBARA, CHAIR
JEAN-LUC BREDAS, VICE CHAIR

- **Keynote Lectures**
  (*Robert Silbey* / Alan J. Heeger / Mostafa El-Sayed)
- **Molecular Electronics**
  (*Aleks Rebane* / Mark Ratner / Dan Ralph / Phaedon Avouris)
- **Ultrafast Dynamics**
  (*Benjamin J. Schwartz* / Villy Sundstrom / Eric Bittner)
- **Interfaces**
  (Bill Salaneck / Carlos Silva / Henning Sirringhaus)
- **Energy and Charge Transport I**
  (*Gregory Scholes* / Yossi Klafter / Veaceslav Coropceanu)
- **Energy and Charge Transport II**
  (*L.D.A. Siebbeles* / Hsin-Feng Meng / Hans B. Brom / Lynn Loo)
- **Nanoparticles and Self Assembly**
  (*Efrat Lifshitz* / A.P.H.J. Schenning / Hiroshi Masuhara)
- **Devices and Materials I**
  (*David Vanden Bout* / Natilie Stingelin-Stutzmann / Tetsuo Tsutsui / George Malliaras / Thierry Verbiest)
- **Chare Injection**
  (Sue Carter / John Marohn)

ELECTRONIC SPECTROSCOPY & DYNAMICS
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 10-15, 2006
FREDERIC MERKT, CHAIR
MARK MARONCELLI &
TIMOTHY ZWIER, CO-VICE CHAIRS

- **Electronic Spectroscopy and Fundamental Physics**
  (*Wim Ubachs* / Martin Quack / Ed Hinds / Jun Ye)
- **Electronic Processes in Condensed Phases**
  (*Majed Chergui* / Todd J. Martinez / Tahei Tahara / Nikolaus P. Ernsting / Rienk van Grondelle)
- **High-Resolution Electronic Spectroscopy**
  (*David W. Pratt* / John P. Maier / Terry A. Miller / Timothy C. Steimle)
- **Biological Molecules**
  (*Donald H. Levy* / Samuel Leutwyler / Bern Kohler / Thomas Rizzo / John Simons)
- **Ultrafast Dynamics and Metrology**
  (*Paul Corkum* / Ferenc Krausz / David Villeneuve / Kjeld Eikema)
- **Single Molecule Electronic Spectroscopy**
  (*Urs P. Wild* / Paul F. Barbara / Lothar Kador / Christian Hübner)
- **Clusters and Imaging**
  (*Elliot R. Bernstein* / Mark Johnson / Mike Ashfold / Wolfgang Ernst / Arthur Suits)
- **Cold Molecules**
  (*Pierre Pillet* / Timothy P. Softley / Gerard Meijer / Peter Barker)
- **Excited State Dynamics**
  (*Robert W. Field* / Thomas F. Gallagher / Helen Fielding / Leticia González / Wolfgang Domcke)

ENDOTHELIAL CELL PHENOTYPES IN HEALTH & DISEASE
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
AUG 6-11, 2006
JOE G.N. GARCIA, CHAIR
THOMAS DANIEL, VICE CHAIR

- **Keynote Lecture**
  (Jordon Pober)
- **Outside-the-Box Perspectives**
  (*William Aird* / George Mensah / Alan Hargens / Jane Maienschein / Ralph Purdy)
- **The Mobile Endothelium**
  (*Robert Hebbel* Shahin Rafii / Catherine Verfaille / Mervin Yoder / Rob Simari)
- **Beyond Angiogenesis - VEGF and the Endothelium**
  (*Hal Dvorak* / Hellmut Augustin / Young Kwon Hong / Norbert Voelkel / Susan Quaggin / Jan Kitajewski)
- **RAGE and the Hetergeneous Endothelium**
  (*David Stern* / Wen-Cheng Xiong / Hiroshi Yamamoto / Ed Conway / Christine Metz)
- **Congenital Abnormalities and the Heterogeneous Endothelium**
  (*Thomas Daniel* / Mikka Vikkula / Dean Li / Michelle Letarte / Christer Betsholtz / Anne Eichmann / Michael Klagsbrun)
- **Organotypic Endothelium in Disease**
  (*Barbara Ballermann* / Napoleone Ferrara / Didier Stainier / Eckhard Lammert / Ondine Cleaver)
- **Heterogeneity in Permeability of the Endothelium**
  (*Troy Stevens* / Elizabetta Dejana / Tanya Mayadas / Tim Hla / Sarah Yuan / William Sessa / Asrar Malik)
- **Engineering the Vasculature**
  (*Gregg Semenza* / Rakesh Jain / Shulamit Levenberg)

ENERGETIC MATERIALS
TILTON SCHOOL
TILTON, NH
JUN 18-23, 2006
CHARLES WIGHT, CHAIR
RUTH DOHERTY, VICE CHAIR

- **Nanoenergetics**
- **Explosive Initiation - Modeling**
- **Explosive Initiation - Experiment**
- **Burn Rate Estimation and Modification**
- **Computation and Simulation - Molecular Scale**
- **Computation and Modeling - Mesoscale**
- **Computation and Modeling - Systems Scale**
- **High Nitrogen Materials**
- **Chemistry Under Extreme Conditions**

ENVIRONMENTAL BIOINORGANIC CHEMISTRY
PROCTOR ACADEMY
ANDOVER, NH
JUN 18-23, 2006
ALISON BUTLER &
BRADLEY TEBO, CO-CHAIRS
ANNE SUMMERS, VICE CHAIR

- **Environmental BioInorganic Chemistry: From the Global to the Molecular Scale**
  (James Penner-Hahn)
- **Marine Bioinorganic Chemistry**
  (Brian Palenik / Neil M. Price / Mary Ann Moran / Mark Hildebrand)
- **Metal Complexation by Microbes and in the Environment**
  (Kenneth N. Raymond / George W. Luther / Katherine Barbeau)
- **Bioinorganic Chemistry of Methanotrophs**
  (Amy C. Rosenzweig / David W. Graham)
- **Microbe-Mineral Interactions**
  (Thomas DiChristina / Yuri Gorby / Arash Komeili / David J. Richardson)
- **Extreme Environments and Toxic Metals**
  (Kenneth H. Nealson / Ronald S. Oremland)
- **Environmental Bioinorganic Chemistry of Manganese**
  (Michael J. Daly / John Bargar / Alexis S. Templeton)
- **Microbes from Diverse Environments**

ENVIRONMENTAL SCIENCES: WATER
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUN 25-30, 2006
ERIC WEBER, CHAIR
BEATE ESCHER, VICE CHAIR

- **Regulatory Processes Controlling Chemical Registration in the US and ECU**
  (*Aldos Barefoot*)

- **Biogeochemistry: Processes Controlling Redox Status in Natural Systems**
  (*Don Macalady* / John Washington / Martial Taillefert / Philippe Van Cappellen)
- **Complex Chemical Mixtures: Presenting New Challenges to the Environmental Scientific Community**
  (*Chad Jafvert* / Rolf Altenburger)
- **Trace Metal Speciation: Role of Sulfide and Organic Ligands**
  (*John Westall* / Steve Cabaniss / Bernd Nowack)
- **Ecotoxicology: Where Environmental Chemistry Meets Effects**
  (*Beate Escher* / Peter Landrum / Kristin Schirmer)
- **Environmental Fate: Bridging Laboratory to Field Studies**
  (*Alan Stone* / Allison MacKay / Linda Lee)
- **Microbial Degradation of Organic Contaminants: Addressing a Significant Area of Uncertainty**
  (Larry Wackett)
- **Environmental Chemistry of Nanomaterials**
  (*Richard Zepp* / Wei-Xian Zhang / Mark Wiesner / John Crittenden)
- **Addressing Environmental Pollution in Third World Countries**
  (*Yu-Ping Chin* / Menachem Elimelech / Stephan Hug)

ENZYMES, COENZYMES & METABOLIC PATHWAYS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 16-21, 2006
SUSAN MILLER & JOHN RICHARD, CO-CHAIRS
SQUIRE BOOKER &
NIGEL RICHARDS, CO-VICE CHAIRS

- **Enzymes in Complex Systems**
  (*Greg Reinhart* / David Cane / Suzanne Walker / Scott Strobel)
- **Enzymes in Disease**
  (*Tod Holler* / Adrian Whitty / Robert Copeland / Walter Ward / Jim Wells)
- **Metal Ions in Catalysis**
  (*Maria Vanoni* / Minae Mure / Amy Rosenzweig)
- **Mechanisms of Enzyme Action**
  (*Dehua Pei* / Kevin Dalby / Eileen Jaffe / Mark Distefano / Debra Dunaway-Mariano)
- **Catalysis at and Across Membranes**
  (*Karen Allen* / Squire Booker / Charles Sanders / Nicole Sampson)
- **Coenzymes in Catalysis**
  (*Bruce Palfey* / Andrea Mattevi / Frank Jordan / Giovanni Gadda / Neil Marsh)
- **Enzymes in Pathways**
  (*Rex Pratt* / Markus Fischer / John Kozarich)
- **Catalysis at and by Nucleic Acids**
  (*Anthony Berdis* / Hiro-Aki Suga / John Burke / Ming-Daw Tsai / Ken Johnson)
- **Frontiers in Enzymology**
  (*Dagmar Ringe* / Joanne Stubbe / Don Hilvert)

FLOW & TRANSPORT IN PERMEABLE MEDIA
PROCTOR ACADEMY
ANDOVER, NH
JUL 30-AUG 4, 2006
MARTIN BLUNT, CHAIR
DANI OR, VICE CHAIR

- **Mathematical and Conceptual Fundamentals of Flow and Transport**
  (*Martin Blunt* / Harvey Scher / Ruben Juanes)
- **Pore-Scale Imaging, Analysis and Modeling**
  (*Brent Lindquist* / *Tad Patzek* / Mark Knackstedt / Dorthe Wildenschild / Kejian Wu / Mohammad Piri)
- **Wetting, Capillarity and Drying**
  (*Pål-Eric Øren* / Jose Bico / Yannis Yortsos)
- **Transport in Biological Systems and Colloids**
  (*Majid Hassanizadeh* / *David DiCarlo* / Ernst Steudle / Markus Flury / Jim Saiers)
- **Reactive Transport**
  (*Dani Or* / Charlie Harvey / Brian Berkowitz)
- **Reservoir Simulation**
  (*Mary Wheeler* / Marco Thiele / Margot Gerritsen / Jef Caers)
- **Observation and Modeling of Flow in Fractured Media**
  (*Abbas Firoozabadi* / Stephan Matthai / David Ponting)
- **Geological Structure from the Pore to the Aquifer Scale and its Impact on Transport**
  (*Graham Fogg* / *Hamdi Tchelepi* / Binayak Mohanty / Steve Bryant / Robert Ritzi)
- **Geological Carbon Storage**
  (*Michael Celia* / Karsten Pruess / Sally Benson)

FUEL CELLS
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 23-28, 2006
BRIAN BENICEWICZ &
JEREMY MEYERS, CO-CHAIRS
BRYAN PIVOVAR &
TOMOYUKI TADA, CO-VICE CHAIRS

- **Membranes**
  (Bryan Pivovar / David Shiraldi / Chris Cornelius)
- **Catalyst Stability**
  (Yang Shao-Horn / Tom Fuller)
- **Alternate Materials**
  (Arumugam Manthiram / Hector Abruno / Karren More)
- **Mass Transport**
  (Matthew Mench / Fritz Prinz / Tom Trabold)
- **Systems**
  (Sathya Motupally)

GRANULAR & GRANULAR-FLUID FLOW
THE QUEEN'S COLLEGE
OXFORD, UK
JUL 23-28, 2006
CHRISTINE HRENYA, CHAIR
ROBERT BEHRINGER, VICE CHAIR

- **Particulate Flows in Nature**
  (*Thorsten Pöschel* / Spyros Pandis / André Brahic)
- **Theory**
  (*Javier Brey* / Sam Edwards / Antoinette Tordesillas / Jim Dufty)
- **Chute Flows**
  (*Michel Louge* / Jim Jenkins / Jim McElwaine)
- **Granular Physics**
  (*Kimberly Hill* / Hayley Shen / Narayanan Menon / Heinrich Jaeger)
- **Geophysical Flows**
  (*Troy Shinbrot* / Steve Sparks / Melany Hunt)
- **Jamming**
  (*V Kumaran* / Michael Cates / Corey O'Hern / Bulbul Chakraborty)
- **Experimental Methods**
  (*Mark Shattuck* / Ricky Wildman / Don Candela)
- **Suspensions**
  (*John Brady* / Tony Ladd / Jeff Morris / Rodrigo Soto)
- **Instabilities and Open Issues**
  (*Tom Mullin* / Ray Cocco / Ben Glasser)

GREEN CHEMISTRY
MAGDALEN COLLEGE
OXFORD, UK
AUG 27-SEP 1, 2006
ROMAS KAZLAUSKAS &
GARY SHELDRAKE, CO-CHAIRS
JAMES HUTCHISON &
JANET SCOTT, CO-VICE CHAIRS

- **Emerging Issues in Green Chemistry**
  (*Terry Collins* / Paul Anastas / Barry Trost)
- **Fine Chemicals from Sustainable Raw Materials**
  (*Jeremy Tomkinson* / Rawle Hollingsworth / James Clark)
- **Photochemistry**
  (Nate Lewis / Michael Oelgemoller)
- **Design of Compounds for Lower Environmental Impact**
  (*Gillian Stephens* / Larry Wackett / Anne-Marie Tillman)
- **Green Process Design**
  (*Buzz Cue* / Eric Beckman)
- **Greener Processes in Ionic Liquids**
  (*Robin Rogers* / Chris Hardacre / Buxing Han)
- **New Reaction Discovery**
  (*C-J. Li* / Jae Sung Lee / Graham Hutchings)
- **Greener Processes in Non-Traditional Solvents**
  (*Joan Brennecke* / Philip Jessop / Pete Licence)
- **Poster Presentations**
  (*Janet Scott* / *Jim Hutchinson*)
- **Chemical Impact on the Environment**
  (*Terry Collins* / J. Peterson Myers)
- **Metal Recovery and Reuse**
  (Dave Bergbreiter / Martin Goosey)
- **New Opportunities in Green Chemistry**
  (*Jim Bashkin* / Wayne Garrison / John Warner)

GROWTH FACTOR SIGNALLING
CONNECTICUT COLLEGE
NEW LONDON, CT
JUL 16-21, 2006
DEBORAH MORRISON, CHAIR
MICHAEL YAFFE, VICE CHAIR

- **Keynote Lecture**
  (Chris Marshall)
- **Growth Factor Signaling Through Receptor Tyrosine Kinases**
  (*Steve Hubbard* / Morrie Birnbaum / Morag Park / Kermit Carraway)

- **Signaling mechanisms Through Scaffolds and Adaptor Proteins**
  (*Roger Davis* / Tony Pawson / John Scott / Gary Koretsky)
- **Signal Integration**
  (*Melanie Cobb* / Dario Alessi / John Blenis / Michael Yaffe)
- **TGF-β Family of Growth Factor Receptors**
  (*Liliana Attisano* / Caroline Hill / Jeff Wrana / Ying Zhang)
- **From Molecules to Networks**
  (*Jim Ferrell* / David Barford / Doug Lauffenberger / Gavin MacBeath)
- **G-Protein Signaling and Cytoskeletal Dynamics**
  (*Dafna Bar Sagi* / Klaus Hahn / Richard Marais / Sheila Thomas)
- **High Throughput Analysis/RNAi Screen and Proteomics**
  (*Tobias Meyer* / Forest White / Mark Vidal / David Sabatini)
- **Neuronal Signaling Mechanisms**
  (*Elena Pasquale* / Ira Daar / Moses Chao / David Ginty)

HEMOSTASIS
COLBY COLLEGE
WATERVILLE, ME
JUL 9-14, 2006
JOSE LOPEZ, CHAIR
PETER NEWMAN, VICE CHAIR

- **Blood Coagulation - A Historical View**
  (*Peter Newman* / Ulla Hedner)
- **Platelet Adhesion**
  (*J. Evan Sadler* / Jorge Di Paola / Miguel Cruz / Zaverio Ruggeri / Andrew Weyrich / Michael Berndt)
- **Anticoagulation**
  (Alan Mast / Gary Gilbert / Susan Lord)
- **ADAMTS-13**
  (*David Ginsburg* / Toshiyuki Miyata / Peter Lenting / Jing-fei Dong / Flora Peyvandi / David Motto)
- **Coagulation**
  (*Paula Tracy* / Sriram Krishnaswamy / Ton Lisman / Reyhan Diz-Kucukkaya / David Gailani)
- **Platelet Signaling**
  (*Lawrence Brass* / Leslie Parise / Yukio Ozaki / Xiao-Ping Du / Alastair Poole / Luigi DeMarco / JoAnn Trejo)
- **Platelets in Inflammation**
  (*Edward Plow* / Daniel Simon / Satya Kunapoli / Cecile Denis / C. Wayne Smith / Barry Coller)
- **Hot Topics**
  (Speakers to be chosen from submitted abstracts)
- **Microparticles**
  (Bruce Furie)

HETEROCYCLIC COMPOUNDS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 2-7, 2006
JOHN MACOR, CHAIR
ERIK SORENSEN, VICE CHAIR

- **Organometallic Approaches to Heterocycles**
  (*Erik Sorensen* / Robert Grubbs / Short Talk / Stephen Buchwald)
- **Methodology for the Synthesis of Heterocyclic Compounds (Part 1)**
  (*Melanie Sanford* & *Brad Henke* / Veronique Gouverneur / Alexander Heim / Dennis Hlasta / Albert Padwa)
- **Heterocyclic Compounds as Natural Products**
  (*Karin Briner* / Patrick Harran / Viresh Rawal)
- **Methodology for the Synthesis of Heterocyclic Compounds (Part 2)**
  (*Stuart McCombie* & *Philip Baran* / Victor Snieckus / Andrew Stamford / Shawn Hitchcock / Dawn George)
- **Catalysis in Heterocyclic Synthesis**
  (*George Mullen* / Michael Krische / Short Talk / Karl Scheidt)
- **Methodology for the Synthesis of Heterocyclic Compounds (Part 3)**
  (*Stephen Godleski* & *Ted Taylor* / David St. Clair Black / Marvin Miller / Jeffrey Bode / Huw M.L. Davies)
- **Directed Heterocyclic Chemistry for the Synthesis of Unnatural Products**
  (*Anthony Cocuzza* / Marc Chapdelaine / Short Talk / Siem Veenstra)
- **Heterocyclic Natural Product Synthesis**
  (*Glenn Micalizio* & *Andrew Degnan* / John Wood / Michael Crimmins / Richard Taylor / Amos Smith III)
- **Perspective on Heterocyclic Chemistry**
  (*Thomas Goodwin* / Short Talk / Paul Reider)

HIGH PRESSURE, RESEARCH AT
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 25-30, 2006
REINHARD BOEHLER, CHAIR
STANLEY TOZER, VICE CHAIR

- **Planetary Interiors**
  (*Bill Nellis* / Guy Masters / David Stevenson)
- **Earth's Mantle and Core: Experiments**
  (*Don Weidner* / Isabelle Daniel / Eiji Ito / Guoyin Shen)
- **Melting at High Pressure: Measurements and Theory**
  (*Choong-Shik Yoo* / Marvin Ross / David Price / Martin Wilding)
- **New High Pressure Phases**
  (*Malcolm McMahon* / Mikhail Eremets / Stanimir Bonev / Olga Degtyareva / Yuichi Akahama)
- **Insulator-Metal Transitions**
  (*Karl Syassen* / Egor Babaev / Ingo Loa)
- **Techniques and New Developments**
  (*Stan Tozer* / Geun Woo Lee / Yogesh Vohra / Li Li / Sebastien Merkel)
- **Diamonds**
  (*Ann Chopelas* / Koen De Hantsetters / Hitoshi Sumiya / Chih-Shue Yan)
- **Shock Compression**
  (*Vladimir Fortov* / Jon Eggert / Tsutomu Mashimo / Gennady Kanel)
- **Frontiers in High Pressure Research**
  (*Isaac Silvera* / John Parise / Neil Ashcroft)

HIGH TEMPERATURE MATERIALS, PROCESSES & DIAGNOSTICS
COLBY COLLEGE
WATERVILLE, ME
JUL 16-21, 2006
BRIAN SHELDON, CHAIR
ELIZABETH OPILA, VICE CHAIR

- **Solid Oxide Fuel Cells: Processes and Materials**
  (*Subhash Singhal* / John Kilner / Anil Virkar)
- **Interfacial Phenomena**
  (*Robert Kao* / C. Barry Carter / Joachim Maier / Izabela Szlufarska)
- **Solid Oxide Fuel Cells: Processes and Materials**
  (*Subhash Singhal* / Meilin Liu / Ellen Ivers-Tiffée)
- **Morphology Evolution and Kinetics in Vapor Deposited Materials**
  (*Ted Besmann* / David Srolovitz / Zhong Lin Wang / James Hannon)
- **Sensors / Small Devices for High Temperature Applications**
  (*Pelagia-Irene Gouma* / Harry Tuller / Carlo Carraro)
- **Computational Modeling for High Temperatures**
  (*Marius Stan* / Patrice Turchi / Susan Sinnott / Austin Chang)
- **High Temperature Oxidation**
  (*Nate Jacobson* / Jochen Marschall / Evan Copeland)
- **Bonding, Chemistry, and Kinetics at High Temperatures**
  (*Klaus Hilpert* / Roger Falcone / Marcelle Gaune-Escard / Carelyn Campbell)
- **Closing Lecture**
  (*Brian W. Sheldon* / Robert Piascik)

HOST-PARASITE INTERACTIONS, BIOLOGY OF
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 25-30, 2006
MICHAEL A. FERGUSON, CHAIR
ELISABETTA ULLU, VICE CHAIR

- **Cell and Developmental Biology**
  (*Keith Gull* / Keith Gull / Keth Matthews / Andy Waters)
- **Organelle Biogenesis**
  (*Steve Hajduk* / Steve Hajduk / Boris Striepen / Geoff McFadden / Cynthia He)
- **Membrane Biology**
  (*Scott Landfear* / Scott Landfear / Norma Andrews / Kasturi Haldar)
- **Host-Cell Invasion**
  (*Barbara Burleigh* / Barbara Burleigh / Dominique Soldati / David Sibley / Ana Rodriguez)
- **Trichomonads and Amoebae**
  (Jorge Tovar-Torres / Zac Cande)
- **Drug Discovery**
  (*Margaret Phillips* / Margaret Phillips / Kip Guy / Bill Charman)
- **Vector Biology**
  (*Anthony James* / Anthony James / Laura Harrington / Paul Bates)
- **Comparative Genomics and Metabolomics**
  (*David Roos* / David Roos / Alan Fairlamb / L. Aravind / Tom Templeton)
- **Gene Expression and Epigenetic Regulation**
  (*Piet Borst* / Piet Borst / Gloria Rudenko / Artur Scherf)

IN VIVO MAGNETIC RESONANCE
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 23-28, 2006
RICHARD BUXTON, CHAIR
JOSEPH ACKERMAN, VICE CHAIR

- **Cells**
  (Michal Neeman / Jeff Bulte / Eric Ahrens)
- **Novel MR Signals and Imaging**
  (Klaus Scheffler / Jurgen Hennig / Graeme Bydder / Daniel Sodickson)
- **Brain Activation**
  (Thomas Liu / Dmitriy Yablonskiy / Fahmeed Hyder)
- **MR Spectroscopy**
  (Oded Gonen / Sarah Nelson / Gerald Shulman / Craig Malloy)
- **Contrast Mechanisms**
  (Michael Garwood / Charles Springer / Elena Vinogradov)
- **MR Extremes**
  (Peter Jezzard / Andrew Webb / Kamil Ugurbil / John Clarke)
- **Hot Topics**
  (Carolyn Mountford)
- **Physiology**
  (Klaas Nicolay / Bruce Damon / Egill Rostrup / Anne-Marie Van der Linden)
- **Diffusion**
  (Richard Buxton / Derek Jones / Jeffrey Neil)

INDUSTRIAL ECOLOGY
THE QUEEN'S COLLEGE
OXFORD, UK
AUG 6-11, 2006
VALERIE THOMAS, CHAIR
FAYE DUCHIN, VICE CHAIR

- **Sustainability: From Theory to Practice**
  (Paul Anastas / Robert Socolow)
- **Environmental Initiatives in Industry**
  (*Michael Bertolucci*)
- **Energy for Sustainability**
  (Marilyn Brown / Klaus Lackner / Jeffrey Siirola)
- **Thermodynamics and Information Theory as Measures of Eco-Efficiency**
  (Tim Gutowski / Bhavik Bakshi)
- **Environmental Impacts of Consumption**
  (*Faye Duchin* / Klaus Hubacek / Carita Niemi / Edgar Hertwich / Yasushi Kondo)
- **Materials and Infrastructure**
  (Arpad Horvath / Duan Weng)
- **Social Science Approaches to Material Flow Analysis**
  (*Kristan Cockerill* / Claudia Binder / Marina Fischer-Kowalski / Annika Carlsson-Kanyama)
- **Industrial Symbiosis**
  (Rene van Berkel / Marion Chertow)

INORGANIC CHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 16-21, 2006
BAHRAM MOASSER, CHAIR
WILLIAM BUHRO, VICE CHAIR

- **The Shape of Things to Come**
  (*George Stanley* / Moungi Bawendi / Raymond Schaak / Sophia E. Hayes)
- **Mechanistic and Organometallic Chemistry**
  (*Andreja Bakac* / John Bercaw / Polly Arnold / Mike Heinekey / Mookie Baik)
- **Coordination and Main Group Chemistry**
  (*Rick Kemp* / Rasika Dias / Philip Power / Matthias Westerhausen)
- **Bioinspired Inorganic Chemistry**
  (*Wayne Gladfelter* / Mary Beth Williams / Yi Lu / Joanna Aizenberg / Patrick Holland)
- **Supramolecular Chemistry**
  (*Kristin Bowman-James* / Kenneth Raymond / Yves Le Mest / Jerry Atwood)
- **Biomedical Inorganic Chemistry**
  (*Bahram Moasser* / Tom Meade / Stephen J. Lippard / Claudia Turro)
- **Nanostructure Synthesis and Application**
  (*John Leman* / Debra Rolison / Larry Lewis / Jillian Buriak)
- **Physical Inorganic Chemistry**
  (*Anna Larsen* / Bill Evans / David Morris / Gordon Yee / Monique Krom)
- **Inorganic Chemistry: Past, Present and Future**
  (*William Buhro* / William Jensen / Nancy Ryan Gray)

INTERFACES, CHEMISTRY AT
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 9-14, 2006
NICHOLAS SPENCER, CHAIR
SCOTT PERRY, VICE CHAIR

- **Opening Lecture**
  (Phil Pincus)
- **Polyelectrolytes and Water: Surface Studies**
  (*Janos Vörös* / Brian Vincent / Mark Rutland / Manfred Heuberger)
- **Molecular-Level Biointeractions**
  (*Sally MacArthur* / Martin Malmsten / Stephanie Allen)
- **Environmental Surface Chemistry**
  (*Gilbert Nathanson* / John Hemminger / Heather Allen / Vicki Grassian / Jeff Roberts / Howard Fairbrother)
- **Exploring Biointerfaces with the Tools of Surface Science**
  (*Dave Castner* / Gabor Somorjai / Marcus Textor / Christine Ortiz / Suzi Jarvis)
- **Surface Science of Chirality**
  (*Andy Gellman* / David Scholl / Rasmita Raval / Eddy Tysoe / Kalle Ernst)
- **Closing Lecture**
  (Barry Ninham)

INTERMEDIATE FILAMENTS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 30-AUG 4, 2006
M. BISHR OMARY, CHAIR
HARALD HERRMANN, VICE CHAIR

- **Biophysics of Intermediate Filaments**
  (*David Parry* / Paul Janmey / Harald Bar / Andreas Hoenger / Karen Ridge)
- **Lamin Biology and Laminopathies**
  (*Gisele Bonne* / Robert Goldman / Colin Stewart / Katherine Wilson / Stephen Young / Georg Krohne / Howard Worman)
- **Intermediate Filaments and Organelle Function**
  (*Carolyn Machamer* / Douglas Green / Yassemi Capetanaki / Thomas Magin / Victor Faundez)
- **Keratins and their Diseases**
  (*Helmut Denk* / Jouni Uitto / Jurgen Schweizer / Pierre Coulombe / Birgitte Lane / Pedro Salas / Masaki Inagaki)
- **Intermediate Filaments, Stress and Signaling**
  (*Milos Pekny* / Tony Hunter / Johanna Ivaska / John Eriksson / Roy Quinlan)
- **Neuronal Intermediate Filament Biology and Diseases**
  (*Ralph Nixon* / Virginia Lee / Don Cleveland / Jean-Pierre Julien / Anthony Brown / Albee Messing / Harish Pant)
- **Intermediate Filament Associated Proteins: From Biology to Disease**
  (*Gerhard Wiche* / Tung-Tien Sun / Kathleen Green / Arnoud Sonnenberg / Roland Foisner)
- **Intermediate Filaments and Tissue Architecture**
  (*Yosef Gruenbaum* / Ueli Aebi / Ronald Liem / Angela Christiano / Lars Norlen / Andrew Kowalczyk / Laurence Etkin)
- **Genomics and Proteomics of Intermediate Filaments**
  (*Larry Gerace* / Robert Hegele / Nicolas Levy / Denise Paulin / Michael Strong)

ION CHANNELS
TILTON SCHOOL
TILTON, NH
JUL 9-14, 2006
STEVE GOLDSTEIN, CHAIR
RICHARD HORN, VICE CHAIR

- **Ligand-Gated Channels**
  (*Henry Lester* / Eric Gouaux / Vasanthi Jayaraman / Robert Oswald)
- **Chloride Channels / Transporters**
  (*Alessio Accardi* / Raimund Dutzler / Michael Pusch / Yun Zhang)
- **Roles in Biology**
  (*Diane Papazian* / Martin Chalifie / Ching Kung / Peter Larsson)
- **Gating I**
  (*Gary Yellen* / Roderick MacKinnon / Eduardo Perozo / Mark Sansom)
- **Permeation**
  (*Wolfgang Nonner* / Claudio Grosman / Karl Magelsby / Benoit Roux)
- **Lipid-Protein Interactions/Folding**
  (Scott Feller / Gunnar von Heijne)
- **Gating II**
  (*Pancho Bezanilla* / Anthony Auerbach / Ramon Latorre / Sarah Lummis)
- **Toxin and Viral Channels**
  (Alan Finkelstein / William DeGrado)
- **Regulation**
  (*John Adelman* / Robert Reenan / Ming Zhou)
- **Short Talks / Late Breaking News**
  (Christopher Ahern / Luis Cuello / Steve Long / Leigh Plant)

IRON-SULFUR ENZYMES
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 11-16, 2006
JOHN PETERS, CHAIR
STEPHEN CRAMER, VICE CHAIR

- **Keynote Lectures**
  (Richard Holm / Rudolf Thauer)
- **Iron-Sulfur Cluster Biosynthesis**
  (Elizabeth Craig / John Golbeck / Michael Johnson / Tracey Rouault)
- **Radical SAM Enzymes**
  (Joan Broderick / Squire Booker / Catherine Drennan / Marc Fontecave)
- **Iron-Sulfur Cluster Chemistry**
  (David Case / Toshiko Ichiye / Marcetta Darensbourg / Stephen Lippard)
- **Hydrogenase**
  (Fraser Armstrong / Juan Fontecilla-Camps / Chris Pickett / Thomas Rauchfuss)
- **Nitrogenase**
  (Patrick Holland / Lance Seefeldt / Akif Teczan)
- **Biosynthesis of Complex Bridged Iron-Sulfur Assemblies**
  (Paul Ludden / Markus Ribbe / Matthew Posewitz / Robert Szilagyi)
- **Others Roles for Iron-Sulfur Proteins and Enzymes**
  (Matthias Boll / Sheila David / Vincent Huynh / Andrew Thomson)
- **Prebiotic Chemistry**
  (Martin Schoonen / Günter Wächtershäuser)

LASER INTERACTIONS WITH MATERIALS
PROCTOR ACADEMY
ANDOVER, NH
AUG 6-11, 2006
DAVE BLANK, CHAIR
WAYNE HESS, VICE CHAIR

The material for this meeting was not available at the time of publication. For the most up-to-date information, please visit the Conference web site:

http://www.grc.org/programs/2006/laserint.htm

LASERS IN MEDICINE & BIOLOGY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 2-7, 2006
RALF BRINKMANN & CHARLES LIN, CO-CHAIRS
PETER SO &
H.J.C.M. STERENBORG, CO-VICE CHAIRS

- **Optics for Clinical Pathology and High Throughput Analysis**
- **Cancer Imaging and Therapy**
- **Optics, Nanotechnology, and Tissue Engineering**
- **Imaging Brain Function and Disease**
- **Optical Techniques for Ophthalmology**
- **New Instrumentation/Methodology**
- **Diabetes: From (Optical) Bench to Bedside**
- **Cellular/Subcellular Imaging and Optical Manipulation**
- **The New Era of Molecular Photomedicine**

LIPOPROTEIN METABOLISM
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 2-7, 2006
MARY SORCI-THOMAS, CHAIR
ROBERT HEGELE & MURRAY HUFF, CO-VICE CHAIRS

- **Emerging Role of Lipids in Development**
  (Robert Steiner / *Laura Wollett* / Thomas Willnow / W. Scott Argraves)
- **Apolipoprotein Structure and Function**
  (Karl Weisgraber / Sean Davidson / Greg Shelness / *Robert Ryan* / Jere Segrest / Michael Oda / Sissel Lund-Katz)
- **HDL, Inflammation and Oxidation in Atherosclerosis**
  (Jay Heineke / Phil Barter / *Roland Stocker* / Linda Curtiss)
- **Genetic Determinants of Lipoprotein Transport**
  (Jake Lusis / Jonathan Smith / Marten Hofker / *Robert Hegele* / Jay Horton / Ruth McPherson)
- **Mechanisms of Hyperlipidemia-Induced Atherosclerosis**
  (Ira Tabas / *Alan Daugherty* / Lynn Hedrick)
- **The Molecular Physiology of HDL Metabolism and Reverse Cholesterol Transport**
  (*Daniel Rader* / Albert Groen / Gerry Waters / Alan Tall / Peter Edwards / Miranda Van Eck)
- **Regulation of Lipoprotein Metabolism by Nuclear Hormone Receptors**
  (Bart Staels / Joyce Repa / *Murray Huff* / Jean Vance)
- **ABC Transporters**
  (Michael Phillips / Michael Hayden / *John Parks* / Yves Marcel / Kerry-Anne Rye / Ashley Vaughan / Cheryl Wellington)
- **Lipid Uptake and Storage**
  (*Ira Goldberg* / Nada Abumrad / Perry Bickel / Rudi Zechner / Ling Li)

LYSOSOMES & ENDOCYTOSIS
PROCTOR ACADEMY
ANDOVER, NH
JUN 25-30, 2006
GREGORY PAYNE, CHAIR
GILLIAN GRIFFITHS, VICE CHAIR

- **Endocytosis and Signal Transduction**
  (*Paolo Di Fiore* / Geraldine Weinmaster / Ivan Dikic)
- **Endocytosis in Cell Physiology and Development**
  (*Pietro De Camilli* / Marco Gonzalez-Gaitan / Timothy Ryan / Juergen Knoblich / Josh Kaplan / Jennifer Lippincott-Schwartz)
- **Structure of Trafficking Machinery Components**
  (*Frances Brodsky* / David Lambright / David Owen / Harvey McMahon)
- **Transport and Sorting in the TGN/Endosome Network**
  (*Marino Zerial* / Juan Bonifacino / Judith Klumperman / Liz Conibear / Harald Stenmark)
- **Mechanisms of Transport Carrier Formation, Targeting, and Fusion**
  (*Margaret Robinson* / Peter McPherson / Sanja Sever / Chris Burd / Linda Hicke)
- **Endocytosis, Lysosomes, and the Cytoskeleton**
  (*Sandra Lemmon* / Christian Merrifield / Lois Weisman)
- **Biogenesis and Disorders of Lysosomes and Lysosome-Related Organelles**
  (*Esteban Dell'Angelica* / Kathleen Collins / Matsinori Fukuda / Paul Saftig)
- **Cell Biology of Pathogen Infection**
  (*Jorge Galan* / Xiaowei Zhuang / Raphael Valdivia)
- **Novikoff Lecture**
  (Sandra Schmid)

MACROMOLECULAR ORGANIZATION & CELL FUNCTION
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
AUG 6-11, 2006
RONALD LYNCH &
STEPHEN OLIVER, CO-CHAIRS
LORANNE AGIUS &
ROBERT BALABAN, CO-VICE CHAIRS

- **Keynote Lecture**
  (*Roger Brent*)
- **Non-Invasive Analysis of the Cell Interior and its Microdomains**
  (*Kevin Brindle* / David Piston / Emily Rothschild / Kevin Fogarty / Gerald Meininger)
- **Metabolomics in Systems Biology: Theory and Experiments**
  (*Douglas Kell* / Uwe Sauer / Daniel Segre / Irina Borodina / Barbara Bakker)
- **Selected Abstracts for Oral Presentation**
  (*Robert Balaban* / *Loranne Agius*)
- **Measurement and Modulation of Protein-Protein Interactions**
  (*Brenda Winkle* / Lynne Regan / Ruth Nussinov)
- **The Mitochondria in Systems Biology**
  (*Robert Balaban* / Berhard Paulsson / Brian O'Rourke / Vamsi Mootha)
- **Subcellular Organization of Cell Signaling**
  (*Paul Insel* / John Scott / Kevin Foskett / Leslie Loew)
- **Analysis and Physico-chemistry of Macromolecular Assemblies**
  (*Maria Luz-Cardenez* / Achilleas Frangakis / Carol Robinson / Len Pagliaro)
- **Quantitative Analysis of Genomic/Metabolomic Data Sets**
  (*Hans Westerhoff* / David Galbraith / Pedro Mendes)
- **Enzyme Localization in the Control of Metabolism**
  (*Loranne Agius* / Simone Baltrusch / Clara Prats / Chris Hardin / Be Wieringa)
- **Round Table Discussion: Understanding Biocomplexity from Both Sides: Proteomics/Metabolomics and Reconstruction**
  (*Steven Oliver* / *Hans Westerhoff*)

MAGNETIC NANOSTRUCTURES
THE QUEEN'S COLLEGE
OXFORD, UK
SEP 3-8, 2006
JAGADEESH MOODERA, CHAIR
STEFAN BLUEGEL, VICE CHAIR

- **Multiferroics**
  (*Agnes Barthelemy* / Ramamurthy Ramesh / Nicola Spaldin)
- **Spin Transfer Nano Oscillators, Spin Torque Diodes**
  (*Robert Buhrmann* / Steve Russek / Fred Mankoff / Yoshishige Suzuki)

- **Electrical Spin Injection into Semiconductors**
(*Hideo Ohno* / Ronnie Jansen / Berend Jonker)
- **Magnetic Molecules and Nanoparticles**
(Roberta Sessoli / Wolfgang Wernsdorfer / Sara Majetich / Benjamin Yellon)
- **Spin Hall effect and Spin Transport in CNT**
(Christian Schonenberger / David Awschalom / Qian Niu)
- **Magnetic Oxide Semiconductors**
(*Tomasz Dietl* / Michael Coey / Scott Chambers)
- **Domain Wall Logic**
(Russel Cowburn)
- **Spin Wave Tunneling and Coherent Tunneling**
(Sergej Demokritov / Evgeny Tsymbal)

MAMMALIAN GAMETOGENESIS & EMBRYOGENESIS
CONNECTICUT COLLEGE
NEW LONDON, CT
JUN 18-23, 2006
MARISA BARTOLOMEI, CHAIR
MICHAEL SKINNER, VICE CHAIR

- **Gamete Maturation and Fertilization**
(*Richard Schultz* / John Eppig / Teresa Woodruff / Robert Braun)
- **Stem Cells: From Gametes to Embryos and Beyond**
(*Peter Donovan* / Janet Rossant / Takashi Shinohara / Haifan Lin / Erika Matunis)
- **Gene Regulation during Gametogenesis and Embryogenesis**
(*Mitch Eddy* / Miles Wilkinson / Kami Ahmad)
- **Meiosis**
(*Paula Cohen* / James Turner / Laurinda Jaffe / Mary Herbert)
- **The ART and Science of Assisted Reproduction**
(*Catherine Racowsky* / Mary Croughan / Ann Thurin Kjellberg / John McCarrey)
- **Epigenetic Regulation of the Germline and Early Embryo**
(*Tamara Davis* / Wolf Reik / Scott Coonrod / Emma Whitelaw)
- **Environmental Impacts on Embryogenesis and Gamete Programming**
(*Mike Skinner* / Patricia Hunt / Matthew Anway / Cheryl Walker)
- **Genetics, Genomics, Proteomics and New Technology**
(Mary Ann Handel / Gregory Kopf)
- **Founders' Forum**
(Rudolf Jaenisch / Davor Solter / John Biggers)

MARINE MICROBES
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 23-28, 2006
DAVID CARON &
ALEXANDRA WORDEN, CO-CHAIRS
CARLOS PEDROS-ALIO, VICE CHAIR

- **Keynote Lectures**
(*Mary Ann Moran* / David L. Kirchman / Sandie Baldauf)
- **Environmental Surveys and Functional Diversity**
(*Gerhard Herndl* / Carlos Pedrós-Alió / Purificación López-García / Laure Guillou)
- **Factors Affecting and Controlling Microbial Interactions and Processes**
(*John Hobbie* / Jed Fuhrman / Farooq Azam)
- **Ecological Insights Through Genomic Approaches**
(*Jonathan Eisen* / Edward DeLong / Mary Ann Moran / Alex Worden)
- **Biotic Interactions - Competition and Predation**
(*Barry Sherr* / Suzanne Strom / Jens Boenigk)
- **Biotic Interactions - Evolution of Form and Function**
(*Rebecca Gast* / Diane Stoecker / Hae Jin Jeong / Evelyn B. Sherr)
- **Ubiquity vs. Endemism: The Distributions of Prokaryotes and Eukaryotes (Round Table Discussion)**
(*Forest Rohwer* / Bland Finlay / Colomban de Vargas / Claire Horner-Devine / Pep Gasol)
- **Modeling Microbial Activities and Interactions**
(Arthur Grossman / David Siegel / T. Frede Thingstad)
- **Evolutionary Outcomes and Synthesis**
(*David Kirchman* / Nicole King / Victor Smetacek)

MECHANISMS OF EPILEPSY & NEURONAL SYNCHRONIZATION
COLBY COLLEGE
WATERVILLE, ME
AUG 6-11, 2006
IVAN SOLTESZ & KEVIN STALEY, CO-CHAIRS
DOUGLAS COULTER, VICE CHAIR

- **New Approaches to the Pathophysiology and Therapy of Epilepsy**
(*Kevin Staley* / *Ivan Soltesz* / Ray Dingledine / Arnold Kriegstein)
- **Epileptogenic Ion Channels**
(*Heinz Beck* / Heinz Beck / Jeff Noebels / Miriam Meisler / Scott Thompson / Christophe Bernard)
- **Epileptogenic Dysgenesis**
(*David Prince* / David Prince / Scott Baraban / Pat Levitt / Peter Crino)
- **Homeostatic Plasticity and Epilepsy**
(*Terry Sejnowski* / Terry Sejnowski / Astrid Prinz / Istvan Mody / David McCormick / John Swann)
- **Structural Reorganization in Epilepsy**
(*Yehezkel Ben-Ari* / Yehezkel Ben-Ari / Carolyn Houser / Tamas Freund / Helen Scharfman / Viji Santhakumar)
- **Hypersynchrony and Non-Linear Dynamics**
(*John Huguenard* / John Huguenard / Steve Schiff / Wim van Drongelen / Brian Litt / John White)
- **Gap Junctions in Epilepsy**
(*Barry Connors* / Barry Connors / Gabor Tamas / Hanna Monyer / Roger Traub)
- **Key Events Underlying Epileptogenesis**
(*Jim McNamara* / Jim McNamara / Jaideep Kapur / Amy Brooks-Kayal / Frances Jensen / Ed Dudek / Greg Holmes)
- **Entorhino-Hippocampal Interplay in Epilepsy**
(*Gyuri Buzsaki* / Gyuri Buzsaki / Richard Miles / Nelson Spruston / Paul Buckmaster)

MECHANISMS OF TOXICITY
COLBY COLLEGE
WATERVILLE, ME
JUL 23-28, 2006
CHARLENE A. MCQUEEN, CHAIR
MARY WALKER, VICE CHAIR

- **Glycogen Synthase Kinase 3ß Phosphorylation: Risks Versus Benefits**
(*Ruth Roberts* / *Ronald Tjalkens* / Ana Martinez / Stuart Aaronson / Charles Ruegg)
- **Chemical Mechanisms of Xenobiotic Bioactivation and Toxicity**
(*Gary Yost* / *Ronald N. Hines* / Paul Hollenberg / Sidney Nelson / Sharon Murphy)
- **Ubiquitin Proteosome System**
(*Elaine Faustman* / *Trevor Archer* / Maria Almira Correia / Richard Pollenz / Azad Bonni)
- **Transporters: Proteins of Emerging Importance in Xenobiotic Disposition and Toxicology**
(*Jose Manautou* / *Nathan Cherrington* / Ronald Oude Elferink / Susan Cole / Curtis Klaassen)
- **Mechanisms of Nucleocytoplasmic Trafficking**
(*Richard S. Pollenz* / *Kenneth S. Ramos* / Bryce Paschal / Walter Watson / Donald DeFranco)
- **Mitochondrial-Mediated Metabolic Diseases**
(*Kendall B. Wallace* / *Rick G. Schnellmann* / William Copeland / Elaine Holmes / Gerald S. Shadel)
- **Fetal Basis of Adult Disease**
(*Mary Walker* / *Kevin Osteen* / Mark Hanson / Gail S. Prins / Nasar Zawia)
- **Cell-Cell Interactions that Mediate Organ System Toxicity**
(*Kim Boekelheide* / *Agnes Kane* / Michael Aschner / Sem Phan / John Richburg)
- **Keynote Speaker**
(*Charlene A. McQueen* / Michael Gallo)

MEDICINAL CHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
AUG 6-11, 2006
JOHN LOWE, CHAIR
GEORGE HARTMAN, VICE CHAIR
LES MCQUIRE, VICE CHAIR ELECT

- **Fragment-Based Drug Design**
(*Alan Stobie* / Martin Stahl / Wolfegang Janke / Ben Davis / Robin Carr)
- **Novel mGluR Targets**
(*Jeff Schkeryantz* / Mike Johnson / Fabriano Gasoparini / Sonia Poli / Jeff Conn)
- **Selective Androgen Receptor Modulators (SARMS)**
(*Mark Duggan* / Duane Miller / Lin Zh / Robert Meissner)
- **Alzheimer's Disease**
(*Jim McCarthy* / Steve Paul / Boyd Harrison / Tim Durham / Philippe Nantermet)
- **Potential New Drugs for the Treatment of Cancer**
(*Jon Wright* / Marcus Boehm / Michael Wendt / Jeffrey Besterman)
- **Novel GPCR Targets**
(*Ginny Ho* / Graeme Semple / Michael Neeb / Carolyn Dzierba / Scott Kuduk)

- **Monoamine Transporters**
  (*Al Robichaud* / Lori Krim Gavrin / Magnus Walter / Derrick Denhart)
- **Special Topics**
  (*Suzanne Stokes*)
- **Chair's Talk**
  (*John Lowe* / John Talley)

MEIOSIS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 11-16, 2006
MIMI ZOLAN, CHAIR
SCOTT KEENEY, VICE CHAIR

- **Synaptonemal Complex 50th Anniversary Celebration**
  (*Pat Pukkila* / Montrose Moses / Denise Zickler / Christa Heyting / Peter Moens)
- **Pre-Meiotic S and Early Meiotic Events**
  (*Doug Bishop* / Alain Nicolas / Gerry Smith / Charles White / Franz Klein / Nancy Hollingsworth)
- **Recombination Mechanisms**
  (*Neil Hunter* / Doug Bishop / Simon Boulton / Michael Lichten / Patrick Sung / Jeff Sekelsky / Dan Camerini-Otero)
- **Meiotic Chromatin and Epigenetics**
  (*Scott Keeney* / Paul Burgoyne / Bill Kelly / Anne Villeneuve / Terry Orr-Weaver / Tom Petes / Deborah Bourc'his)
- **Regulation, Cell Cycle Control, and Gametogenesis**
  (*Sharon Bickel* / Angelika Amon / Paula Cohen / Masayuki Yamamoto / Scott Hawley / Akira Shinohara / Noriyoshi Sakai)
- **Pairing, Chromosome Dynamics, and Segregation**
  (*Denise Zickler* / Nancy Kleckner / Abby Dernburg / Zac Cande / Gareth Jones / Adela Calvente / Dean Dawson)
- **Kinetochores, Meiotic Cohesion and Spindles**
  (*Angelika Amon* / Yoshi Watanabe / Pat Hunt / Bruce McKee / Sharon Bickel / Kim McKim / Frank McNally)
- **Crossover Control**
  (*Nancy Hollingsworth* / Frank Stahl / Scott Keeney / Barbara Meyer / Neil Hunter / Bernard de Massy)
- **Evolution of Meiosis and Sex Chromosomes**
  (*Mimi Zolan* / John Logdson / David Page / Fernando Pardo-Manuel de Villena / David Mark Welch / Bryant McAllister)

MEMBRANE TRANSPORT PROTEINS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
AUG 13-18, 2006
JONATHAN JAVITCH, CHAIR
LYDIA AGUILAR-BRYAN, VICE CHAIR

- **Keynote Lecture**
  (Roderick MacKinnon)
- **Channels: Structure and Mechanism**
  (*Al George* / *Arthur Karlin* / Diane Papazian / Ehud Isaacoff / Alessio Accardi)
- **Channels in Disease**
  (*Al George* / *Arthur Karlin* / Al George / Peter Mohler / Ted Cummins)
- **Primary Transporters: Structure and Mechanism**
  (*Robert Tampé* / *Helen Hobbs* / Peter Dimroth / Jue Chen / Heather Pinkett)
- **Primary Transporters in Disease**
  (*Robert Tampé* / *Helen Hobbs* / Joe Bryan / Jack Oram / Helen Hobbs / Kazu Ueda / Robert Tampé)
- **Secondary Transporters: Structure and Mechanism**
  (*Gary Rudnick* / Eric Gouaux / Ron Kaback / Etana Padan)
- **Secondary Transporters in Disease**
  (*Gary Rudnick* / Randy Blakely / Kevin Staley / Gajja Salomons / Elena Bagley)
- **Regulation of Membrane Transport Proteins**
  (*Aurelio Galli* / Cecilia Canessa / Ulrik Gether / Melanie Cobb)
- **You Aren't What You Eat Without Membrane Transport Proteins**
  (*Lydia Aguilar Bryan* / Nancy Carrasco / Bernard Thorens / Manuel Palacin)

MEMBRANES: MATERIALS & PROCESSES
COLBY-SAWYER COLLEGE
NEW LONDON, NH
AUG 6-11, 2006
GLENN LIPSCOMB &
MATTHIAS WESSLING, CO-CHAIRS
PETER PINTAURO &
ANDREW ZYDNEY, CO-VICE CHAIRS

- **Keynote Lecture**
  (Don Paul)
- **Micro-Engineered Membranes**
  (*Matthias Wessling*)
- **Nanocomposite Membranes**
  (*Eva Marand*)
- **Inorganic Membranes**
  (*Theo Tsotsis*)
- **Membranes in Tissue Engineering**
  (*Y.M. Lee*)
- **Solute-Membrane Interactions**
  (*John Pellegrino*)
- **Membrane Critical Flux**
  (*Pierre Aimar*)
- **Water Treatment Membranes and Processes**
  (*Isabel Escobar*)
- **Membrane Surface Modification**
  (*Mathias Ulbricht*)

MEMS TECHNOLOGY & BIOMEDICAL APPLICATIONS
CONNECTICUT COLLEGE
NEW LONDON, CT
JUN 25-30, 2006
RAFAEL KLEIMAN, CHAIR
TEJAL DESAI, VICE CHAIR

- **Biologically Inspired MEMS Techniques**
- **Novel MEMS Fabrication Techniques**
- **Novel Materials for BioMEMS**
- **MEMS and BioMEMS Sensors**
- **Microfluidics and Biofluidics**
- **Integration and Lab-on-a-Chip Devices**
- **Biocompatibility for BioMEMS**
- **Implantable Devices**
- **Applications in Human Health**

METABOLIC BASIS OF ECOLOGY
BATES COLLEGE
LEWISTON, ME
JUL 9-14, 2006
PABLO MARQUET & VAL SMITH, CO-CHAIRS
DANIEL COSTA &
ROBERT STERNER, CO-VICE CHAIRS

- **The Metabolic Basis of Ecology and Evolution**
  (*Pablo Marquet* / *Val Smith* / James Brown / Eörs Szathmáry)
- **The Big Picture: Flows of Energy and Materials Across Time, Space and Levels of Organization**
  (*Peter Reich* / Dag Hessen / Carlos Duarte / Andrew Allen / Christopher Klausmeier)
- **Metabolism, Energy Budgets, and Elemental Dynamics**
  (*Susan Kilham* / Ursula Gaedke / Steve Chown / Bas Kooijman)
- **Energy and Materials in Cellular Systems**
  (*Jessica Green* / Tom Kirkwood / Roberto Chignola / Zoe Finkel / John Raven)
- **Energy and Materials in Organisms**
  (*Francisco Bozinovic* / Robert Ricklefs / Emily Carrington / Adam Kay)
- **Energy and Materials in Food Webs**
  (*David Breshears* / Joel Cohen / Michel Loreau / Kevin McCann / Robert Poulin)
- **Metabolic Perspectives in Community Structure and Dynamics**
  (*Steve Hubbell* / David Currie / Brian Enquist / Simon Jennings)
- **Metabolism and Stoichiometry in Evolution**
  (*Ray Huey* / Janet Siefert / Kaustuv Roy / Ted Garland)
- **Future Directions**
  (*Jamie Gillooly* / Robert Holt / Mark Ritchie)

METALS IN MEDICINE
THE QUEEN'S COLLEGE
OXFORD, UK
JUL 9-14, 2006
PETER CARAVAN & PETER SADLER, CO-CHAIRS
SONYA FRANKLIN, VICE CHAIR

- **Special Lecture**
  (H. Allen O. Hill)
- **Chairs' Session**
  (*Peter Caravan* / *Peter J. Sadler* / Bob Williams / George McLendon)
- **Antivirals and Antimicrobials**
  (*Wiley Youngs* / Simon Silver / Carolyn I. Cannon / Luigi Marzilli / Simon Fricker)
- **Metals and Apoptosis: Therapeutic Implications**
  (*Larry Boise* / Milan Vasak / Colin Duckett / Zhu Chen)
- **Anticancer Complexes**
  (*Jan Reedijk* / Gianni Sava / Eric Meggers / Bernhard Keppler / Dolores Fregona)
- **Metals and Magnetic Resonance Imaging**
  (*Silvio Aime* / Thomas Meade / Alan Koretsky / Claire Corot)
- **Anti-Diabetic Metal Complexes**
  (*Chris Orvig* / Debbie C. Crans / Dieter Rehder / Joan J. Guinovart / David L. Brautigan)
- **Phototherapeutic and Photodiagnostic Agents**
  (*Kazuko Matsumoto* / Jeffrey Zaleski / David Parker / Stephane Petoud)

- **Radiopharmaceuticals**
  (*Roger Alberto* / John F. Valliant / Shuang Liu / Jon Zubieta / Hans-Juergen Wester)
- **Vice-Chair's Session**
  (*Sonya Franklin* / Hanns-Joachim Weinmann)

MICROBIAL STRESS RESPONSE
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 9-14, 2006
PATRICIA KILEY, CHAIR
CHESTER PRICE, VICE CHAIR

- **Dissecting Regulatory Networks**
  (*Mark Goulian* / Mustafa Khammash / Philippe Cluzel / Ned Wingreen / Manuel Llinas)
- **General Stress Responses**
  (*Frederick Neidhardt* / Thomas Silhavy / Carol Gross / Tania Baker / Kenn Gerdes / Regine Hengge)
- **Sensing of DNA Replication and Damage**
  (*Michael Cox* / Susan Lovett / Paul Russell / Graham Walker / Alan Grossman)
- **Survival of Microbes in Hosts**
  (*Chester Price* / Abraham Sonenshein / Eduardo Groisman / Michele Swanson / Michael Jennings)
- **Survival of Microbes in Nature**
  (*Dianne Newman* / Edward DeLong / Victor de Lorenzo / Michael Laub)
- **Plasticity in Adaptive Mechanisms**
  (*Timothy Donohue* / Susan Gottesman / Elizabeth Campbell / Kevin Gardner)
- **Oxidative Stress Responses**
  (*Gisela Storz* / Rowena Matthews / James Imlay / Stephen Spiro)
- **Global Adaptation to Stress**
  (*Mitchell Singer* / Richard Losick / Heidi Kaplan / Mark Buttner)
- **Stress and Metals**
  (*Tricia Kiley* / John Helmann / Thomas O'Halloran / Alistair McEwan)

MICROBIAL TOXINS & PATHOGENICITY
PROCTOR ACADEMY
ANDOVER, NH
JUL 16-21, 2006
DRUSILLA BURNS, CHAIR
VICTOR DIRITA, VICE CHAIR

- **Host-Pathogen Interactions**
  (*Virginia Miller* / William Goldman / Hattie Gresham / Manuel Amieva)
- **Genomics and Gene Regulation**
  (*Peggy Cotter* / Andrew Camilli / David Relman / Michael Gilmore / Eduardo Groisman)
- **Intracellular Pathogens**
  (*Michele Swanson* / John Brumell / Barbara Burleigh / Mary O'Riordan)
- **Toxins: Structure, Function, and Mechanism of Action**
  (*Joseph Barbieri* / Roman Melnyk / Karla Satchell / Giampietro Schiavo / Gudula Schmidt)
- **Advancing Technologies and Approaches**
  (*Erik Hewlett* / Darren Higgins / Julian Parkhill)
- **Toxins, Effectors, and the Cell**
  (*James Bliska* / Craig Roy / Christoph Dehio / Daniel Kalman / Wolf-Dietrich Hardt)
- **Pathogenic Strategies**
  (*Joanne Engel* / Stephen Lory / Olaf Schneewind / Brett Finlay)
- **Host Response to Infection**
  (*Michael Starnbach* / Karen Elkins / Patrick O'Farrell / JoAnne Flynn / Douglas Golenbock)
- **Cellular Microbiology**
  (*Drusilla Burns* / Philippe Sansonetti / Ralph Isberg)

MITOCHONDRIA & CHLOROPLASTS
MAGDALEN COLLEGE
OXFORD, UK
AUG 13-18, 2006
MICHAEL YAFFE, CHAIR
JEAN-DAVID ROCHAIX, VICE CHAIR

- **DNA Replication and Expression**
  (Gerald Shadel / Laurie Kaguni / David Stern / Sally MacKenzie)
- **Protein Import**
  (Trevor Lithgow / Arsenio Villarejo / Klaus Pfanner / Norbert Rolland / Ophry Pines / Colin Robinson)
- **Organelle Movement and Morphology**
  (Benedikt Westermann / Maureen Hanson / Peter Hollenbeck / Masamitsu Wada)
- **Protein Complex Assembly and Proteolysis**
  (Alex Tzagaloff / Doron Rapaport / Francis-Andre Wollman / Christiane Funk / Thomas Langer / Elzbieta Glaser)
- **Cofactor Biosynthesis and Metal Homeostasis**
  (Catherine Clarke / Jerry Kaplan / Sabeeha Merchant / Roland Lill)
- **Organelle Division and Fusion**
  (Katherine Osteryoung / Janet Shaw / Simon Moller / Rob Jensen / David Chan / Nobuhiro Tsutsumi)
- **Disease Mechanisms**
  (Massimo Zeviani / William Copeland / Antonio Zorzano / Eric Shoubridge)
- **Regulation and Signaling**
  (Ronald Butow / Klaus Apel / Avi Danon / Lee Sweetlove / Rashu Seth)
- **Development and Aging**
  (Barbara Conradt / Enzo Nisoli / Jane Langdale)

MOLECULAR & CELLULAR BIOENERGETICS
PROCTOR ACADEMY
ANDOVER, NH
JUN 11-16, 2006
STANLEY DUNN, CHAIR
FEVZI DALDAL &
DAVID NICHOLLS, CO-VICE CHAIRS

- **Structures and Coupling Mechanisms in Membrane Transport Systems**
  (*Frances Sharom* / Etana Padan / Amy Davidson / Robert Stroud)
- **Structure and Function of F-ATP Synthase and V-ATPase**
  (*David Mueller* / Thomas Meier / John Walker / Anil Koul)
- **Single Particle Analysis of ATP Synthase Rotary Mechanism**
  (*Wolfgang Junge* / Masamitsu Futai / Hiroyuki Noji / Wayne Frasch)
- **Structure and Function of Respiratory Complexes**
  (*Shelagh Ferguson-Miller* / Bernard Trumpower / Robert Gennis / Joel Weiner)
- **Biosyntheis and Maturation of Bioenergetic Complexes**
  (*Sharon Ackerman* / Rosemary Stuart / Tom Fox / Dennis Winge)
- **Poster Workshops**
  (*Peter Brzezinski* / *Brian Cain* / *Karlett Parra-Belky* / *Immo Scheffler*)
- **Formation and Function of Supercomplexes**
  (*Peter Pedersen* / Jean Velours / Hans-Peter Braun / Miriam Greenberg)
- **Mitochondria, Free Radicals and Cell Signalling**
  (*Guy Brown* / David Kramer / Enrique Cadenas / Gary Fiskum / Anthony Segal)
- **Regulation of V-ATPase**
  (*Michael Forgac* / Sylvie Breton / Patricia Kane / Stephen Gluck)

MOLECULAR & CELLULAR NEUROBIOLOGY
HONG KONG UNIVERSITY OF
SCIENCE & TECHNOLOGY
HONG KONG, CHINA
JUN 11-16, 2006
LI-HUEI TSAI, CHAIR
LOUIS REICHARDT, VICE CHAIR

- **Neuronal Signaling in Transport and Plasticity**
  (*Louis Reichardt* / Bill Mobley / Kelsey Martin / Michael Fainzilber)
- **Neurogenesis and Neuronal Motility**
  (*Yi Sun* / Christopher Walsh / Juergen Knoblich / Rosalind Segal)
- **Establishment of Neuronal Network**
  (*Yi Rao* / Holly Cline / Yishi Jin / Yuh Nung Jan)
- **Synaptic Transmission I**
  (*Kang Shen* / Tom Sudhof / Nancy Ip / Ling-Gang Wu)
- **Synaptic Transmission II**
  (Lily Jan / Atsushi Miyawaki / Josh Huang)
- **Molecular Basis of Neurological Diseases**
  (*Fen-Biao Gao* / Marc Caron / Susan Ackerman / John Trojanowski / Virginia Lee)
- **Plasticity of Neurons I**
  (*Bai Lu* / Morgan Sheng / Tobias Bonhoeffer / Martha Constantine-Paton)
- **Plasticity of Neurons II**
  (Mu-ming Poo / Roger Nicoll / Rick Huganir)
- **Neuronal Communications and Behavior**
  (*John Ngai* / Liqun Luo / Barry Dickson / Bob Horvitz)
- **Alexander M. Cruickshank Lecturer**
  (Linda Buck)

MOLECULAR BASIS OF MICROBIAL ONE-CARBON METABOLISM
MAGDALEN COLLEGE
OXFORD, UK
AUG 6-11, 2006
CORNELIUS FRIEDRICH, CHAIR
STEPHEN RAGSDALE, VICE CHAIR

- **C-1 Genomes**
  (*Dan Arp* / Mary Lidstrom / Karen Nelson / Harald Jensen)

- **Methanogenesis**
  (*Madeline Rasche* / Joseph Krzycki / Christoph Hagemeier / Uwe Deppenmeier / Evert Duin)
- **Mechanisms and Regulation of CO_2-Fixation**
  (*Robert Tabita* / Cheryl Kerfeld / William Whitman / Simona Romagnoli)
- **Methyl- and Methanotrophy**
  (*Howard Dalton* / Amy Rosenzweig / Sunney Chan / Alan DiSpirito / Julia Vorholt / Colin Murrell)
- **Anaerobic Methane Oxidation**
  (*Samantha Joye* / Antje Boetius / Rolf Thauer)
- **C-1 Metabolism, Ecology, Physiology and the Environment**
  (*Gary King* / Barbara Campbell / Thomas Hanson / Robert White / Ralf Conrad)
- **Acetogenesis and CO Metabolism**
  (*Ortwin Meyer* / Holger Dobbek / Astrid Pelzmann / David Grahame / Jared Leadbetter)
- **Autotrophy and Chemolithotrophy**
  (*Bärbel Friedrich* / Masaharu Ishii / Georg Fuchs / Oliver Lenz / Martin Klotz / Mike Jetten / Lisa Stein)
- **C-1 Perspectives**
  (*Cornelius Friedrich* / Ludmilla Chistoserdova / Hendrik Schaefer / Biswarup Mukhopadhyay / Stephen Ragsdale)

MOLECULAR CELL BIOLOGY
TILTON SCHOOL
TILTON, NH
JUL 2-7, 2006
ERIN O'SHEA, CHAIR
JODI NUNNARI, VICE CHAIR

- **Post-Translational Regulation of Protein Function**
  (Brenda Schulman / Wade Harper / Chris Lima)
- **Regulation of Cell Growth**
  (Bruce Edgar / David Sabatini / Ted Powers / Jon Warner)
- **Novel Tools to Study Cellular Function**
  (Alice Ting / Natalie Ahn / Mats Gustafsson / Tom Kirchhausen)
- **Evolution**
  (Harmit Malik / Jeff Boeke / Andrew Murray / Roy Kishony)
- **Cell Biology of Disease**
  (Wes Sundquist / Larry Goldstein / Mina Bissell / David Chan / Elena Rugarli)
- **Roles for RNAs in Cellular Regulation**
  (Victor Ambros / Danesh Moazed / Rachel Green / Kathy Collins)
- **Membrane Dynamics: Regulation of Membrane Structure and Composition**
  (Harvey McMahon / Randy Schekman / Ben Glick / Jennifer Lippincott-Schwartz)
- **Epigenetic Regulation**
  (Jeannie Lee / Barbara Meyer / Brendan Cormack / Steve Henikoff)
- **Regulation of Size and Structure of Cellular Structures and Organelles**
  (Jodi Nunnari / David Ron / Bill Wickner / Arash Komeili / Wallace Marshall)

MOLECULAR MECHANISMS IN LYMPHATIC FUNCTION & DISEASE
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
SEP 3-8, 2006
KARI ALITALO, CHAIR
GEERT SCHMID-SCHONBEIN, VICE CHAIR

- **Lymphangiogenesis - Basic Mechanisms**
  (*Marc Achen* / Peter Carmeliet / Michael Detmar)
- **Lymphatic Endothelium**
  (*Elisabetta Dejana* / Gou Young Koh / Hellmut Augustin)
- **Development of the Lymphatic Vascular System**
  (*Guillermo Oliver* / Anne Eichmann / Jan Kitajewski)
- **Maturation of the Lymphatic Vessels**
  (*Christer Betsholtz* / Gavin Thurston / Tatiana Petrova)
- **The Interstitium, Lymph Formation and Propulsion**
  (*Geert Schmid-Schönbein* / David Zawieja / Melody Swartz)
- **Pathogenesis of Lymphatic Vascular Disease**
  (*Miikka Vikkula* / Peter Mortimer / Stanley Rockson)
- **Lymphatic Vessels in Inflammation**
  (*Dontscho Kerjaschki* / Donald McDonald / David Jackson)
- **Lymphatic Metastasis**
  (*Rakesh Jain* / Mihaela Skobe / Gerhard Christofori)
- **Therapeutic Aspects**
  (*Erkki Ruoslahti* / Bronek Pytowski / Seppo Yla-Herttuala)

MOLECULAR THERAPEUTICS OF CANCER
THE QUEEN'S COLLEGE
OXFORD, UK
JUL 16-21, 2006
ALAN EASTMAN, CHAIR
PHILLIP DENNIS, VICE CHAIR

- **Targeting Lipogenic Pathways in Tumors**
  (*Johannes Swinnen* / William Kinlaw / Ruth Lupu)
- **Developmental Genes and their Therapeutic Potential**
  (*James Winkler* / David Robbins / Fred de Sauvage / Mariann Bienz)
- **Gene Therapy for Cancer: Problems and Progress**
  (*Michael Barry* / Stephen Russell / Alexander Kolykhalov)
- **Cell Cycle Checkpoint Regulation**
  (*Adrian Senderowicz* / Bernard Ducommun / Kenna Anderes / Anthony Shields)
- **DNA Damage and Repair Pathways**
  (*Hilary Calvert* / Graeme Smith / Richard Kennedy)
- **Stem Cells and Differentiation**
  (*George Studzinski* / Andreas Trumpp / Tessa Holyoake / Donald L. Trump)
- **When Will Molecular Prognosis Become Relevant to the Patient?**
  (*Martine Piccart* / Charles Perou / Heidi Greulich)
- **Protein Phosphatases as Potential Therapeutic Targets**
  (*John Lazo* / Wiljan Hendriks / Johannes Rudolph / Daimark Bennett)
- **Nanotechnology in Diagnosis and Treatment of Cancer**
  (Naomi Halas)

MULTIPHOTON PROCESSES
TILTON SCHOOL
TILTON, NH
JUN 11-16, 2006
ROBERT JONES, CHAIR
HENRIK STAPELFELDT, VICE CHAIR

- **Single-Cycle and Attosecond Pulses**
  (*Pierre Agostini* / Steve Harris / Mette Gaarde / Zenghu Chang)
- **Molecular Spectroscopy**
  (Tobias Brixner / Tim Zwier / Thomas Schultz)
- **Ultrafast Molecular Probes**
  (*David Villeneuve* / Margaret Murnane / Dwayne Miller / Jon Marangos)
- **High Intensities**
  (*Barry Walker* / Reinhard Dorner / Lars Madsen)
- **Controlling Light**
  (*Phil Bucksbaum* / Jun Ye / Yaron Silberberg / Ursula Keller)
- **Ultrafast and High Intensity X-Rays**
  (*Linda Young* / Tim Laarman / Robin Santra)
- **Attosecond Science**
  (*Andre Bandrauk* / P. Corkum / Marc Vrakking / Gerhard Paulus)
- **Quantum Control**
  (*Tamar Seideman* / Tom Weinacht / Jonathan Underwood / Robert Levis)

MUSCLE:
EXCITATION / CONTRACTION COUPLING
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 4-9, 2006
SUSAN HAMILTON, CHAIR
KURT BEAM, VICE CHAIR

- **Structural Analysis of ECC Proteins**
  (*Angela Dulhunty* / *Terry Wagenknecht* / Montserrat Samso / Wah Chiu / Clara Franzini-Armstrong)
- **Modulators of SR Calcium Release**
  (*Cecilia Hidalgo* / *Graham Lamb* / Gerhard Meissner / Andrew Marks / Derek Laver)
- **DHPR-RYR Interactions**
  (*Paul Allen* / *Bernard Flucher* / Manfred Grabner / Henry Colecraft / Nancy Lorenzon)
- **Regulation of SR Calcium Release**
  (*Eduardo Rios* / *Steve Hollingworth* / Hepeng Cheng / Sandor Gyorke / Donald Bers / Knox Chandler)
- **Excitation-Transcription Coupling**
  (*Ricardo Dolmetsch* / *Martin Schneider* / Eric Olsen / Jeff Molkentin)
- **Other Contributors to the Regulation of Intracellular Calcium Homeostasis**
  (*Isaac Pessah* / *Mike Fill* / David Clapham / Richard Lewis / Nagomi Kurebayashi / Francesco Zorzato)
- **Muscle Disease**
  (*Robert Dirksen* / *Frank Lehmann-Horn* / Francesco Muntoni / David MacLennan / Kate Bushby)
- **Muscle Membrane Damage and Repair**
  (*Kevin Campbell* / *Osvaldo Delbono* / Jean-Marie Gillis / David Allen / Paul McNeil / Renzhi Han)
- **Roles for RYRS in Other Tissues**
  (*Mark Nelson* / *John Walsh* / Mike Kotlikoff / Valerie DeCrescenzo)

MUSCULOSKELETAL BIOLOGY & BIOENGINEERING
PROCTOR ACADEMY
ANDOVER, NH
JUL 23-28, 2006
CYRIL FRANK, CHAIR
ROCKY TUAN, VICE CHAIR

- **Background: Clinical Needs & Clinical Controversies in Joint Repair** (*Stefan Lohmander* / Lars Engebretsen / Ewa Roos)
- **Tissue Engineering I - The Science: How Do We Evaluate Success?** (*David Butler* / *Jack Lewis* / Scott Tashman / Braden Fleming / Dawn Elliott / Marc Levenston / Bob Guldberg / Al Banes)
- **Tissue Engineering II - The Controversies and Next Steps Toward Success** (*Tony Ratcliffe*)
- **Tissue Engineering III - The Science: Cells, Tissues, Scaffolds, Stresses & Strains** (*David Kaplan*)
- **Tissue Engineering IV - The Controversies and Next Steps Toward Success** (*Gordana Vunjak-Novakovic*)
- **Targeting Joint Repair I - The Science Markers, Methods, Therapeutic Approaches** (*Robin Poole*)
- **Targeting Joint Repair II - The Controversies and Next Steps Toward Success** (*David Hart*)
- **Knockout Models For Understanding Repair and Regeneration - The Science Markers, Methods and Considerations** (*Linda Sandell*)
- **The Fun of Science**

MUTAGENESIS
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 6-11, 2006
SUE JINKS-ROBERTSON, CHAIR
ROGER WOODGATE, VICE CHAIR

- **Keynote Lectures** (Josef Jiricny / Thomas Kunkel)
- **Fidelity of DNA Synthesis** (*Joann Sweasy* / Paul Modrich / Wei Yang / Roel Schaaper)
- **Microbial Mutagenesis** (*Pat Foster* / Miroslav Radman / Jeffrey Miller)
- **Bypass of DNA Lesions** (*Alan Lehmann* / Robert Fuchs / Errol Friedberg / Shunichi Takeda)
- **Transcription and Genetic Stability** (*Ashok Bhagwat* / Paul Doetsch / Jesper Svestrup)
- **Programmed Mutagenesis** (*Patricia Gearhart* / Nancy Maizels / Myron Goodman / Reuben Harris)
- **Chromosomal Mutations** (*Thomas Petes* / Keith Derbyshire / Christopher Pearson)
- **Control of Mutagenic Processes** (*Stefan Jentsch* / Hannah Klein / Steve Elledge / Thomas Wilson)
- **Mutagenesis and Human Disease** (*Judith Campisi* / Alan d'Andrea / Tomas Prolla)

NANOSTRUCTURE FABRICATION
TILTON SCHOOL
TILTON, NH
JUL 16-21, 2006
THERESA MAYER, CHAIR
DAWN BONNELL, VICE CHAIR

- **Nanoscale Materials and Systems** (Chris Murray / Chad Mirkin)
- **Nanoelectronics: Top-Down Meets Bottom-Up** (Lars Samuelson / Joerg Appenzeller)
- **Nanobiosystems** (Jim Heath / Henry Hess)
- **Nanopatterning and Metrology** (Alex Liddle)
- **Graphene and Molecular Electronics** (Philip Kim / Robert Walklow)
- **Self-Assembled Nanostructures** (Cathy Murphy / Kristen Ficthorn / Chris Schafmeister)
- **Nano-Optics** (Teri Odom / Jia Chen)
- **Nanofluidics and Mechanics** (Kamil Ekinci / Abe Stroock)
- **Selected Abstracts for Oral Presentation** (*Dawn Bonnell*)

NATURAL PRODUCTS
TILTON SCHOOL
TILTON, NH
JUL 23-28, 2006
FREDERICK LUZZIO, CHAIR
DAVID UEHLING, VICE CHAIR

- **Biological, Bioorganic, Biosynthetic Chemistry** (David E. Cane / John W. Frost / Jacqueline Gervay-Hague / Linda C. Hsieh-Wilson / Seiichi P.T. Matsuda / Gary Posner)
- **Marine Natural Products** (Bill J. Baker / Mark T. Hamann / Peter Northcote)
- **Medicinal, Process Chemistry** (Ellen W. Baxter / Joe Shih / Robert A. Volkmann / Cynthia Parrish)
- **Organic Synthesis, Synthetic Methods, Total Synthesis** (Anthony G.M. Barrett / Robert K. Boeckman, Jr. / Michael A. Calter / Daniel L. Comins / James M. Cook / Arun K. Ghosh / Dieter Enders / David A. Evans / Philip L. Fuchs / Thomas R. Hoye / Marisa C. Kozlowski / Christina Moberg / Glenn C. Micalzio / Stephen Pyne / Melanie S. Sanford / Steven M. Weinreb)

NEURAL DEVELOPMENT
SALVE REGINA UNIVERSITY
NEWPORT, RI
AUG 20-25, 2006
HOLLIS CLINE, CHAIR
SAMUEL PFAFF, VICE CHAIR

- **Stem Cells** (Gordon James Fishell / William A. Harris / Arnold R. Kriegstein)
- **Transcriptional/Translational Control** (Gail Mandel / Kelsey Martin / Anirvan Ghosh / David Ginty)
- **Patterning/Mapping** (Heinrich Reichert / Kang Shen / Louis F. Reichardt / Liqun Luo / David Feldheim / Frances Lefcort)
- **Synaptogenesis** (Peter Scheiffele / Kim McAllister / Franck Polleux / Akira Chiba)
- **Neuron-Glia Interactions** (Ben Barres / Erik Ullian)
- **Development of Circuits** (Stephen Smith / Michael J. O'Donovan / Silvia Arber / Lynn Landmesser / Lisa Goodrich / Josh Huang / Chinfei Chen)
- **Genes to Behavior** (Elly Nedivi / Piali Sengupta / David Anderson / Herwig Baier / Cori Bargmann / Tim Tully)
- **Disease Models** (Linda Van Aelst / Chris Walsh)

NOX FAMILY NADPH OXIDASES
LES DIABLERETS CONFERENCE CENTER
LES DIABLERETS, SWITZERLAND
OCT 15-20, 2006
KARL-HEINZ KRAUSE, CHAIR
WILLIAM NAUSEEF, VICE CHAIR

- **Keynote Lecture** (Dave Lambeth)
- **NOX Structure** (Kathrin Rittinger / Al Jesaitis)
- **NOX: Cells and Proteins** (Hideki Sumimoto / Bob Clark / Françoise Morel / Ulla Knaus / Tom Leto / Barry Goldstein)
- **Dual Oxidases** (Corinne Dupuy)
- **NOX and GTP-Binding Proteins** (Gary Bokoch / Elisabeth Ligeti / Edgar Pick)
- **NOX Deficiency in Mice and Men** (Mary Dinauer / Botond Banfi / Chihiro Yabe-Nishimura)
- **NOX and Electrogenic Transport** (Tony Segal / Nicolas Demaurex / Tom DeCoursey)
- **NOX in Specific Organ Systems** (Kathy Griendling / Rhian Touyz / Kazuhito Rokutan / David Brenner / Dieter Häussinger)
- **NOX Outside of Mammals** (Klaus Apel / Miklos Geiszt)
- **Oral Presentation of Selected Abstracts**

NUCLEAR CHEMISTRY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 4-9, 2006
ROY LACEY, CHAIR
AUGUSTO MACCHIAVELLI, VICE CHAIR

- **Nuclear Synthesis, and Nuclear Structure with RIB's**
- **Nuclear Structure & Isospin in Reactions**
- **Isospin Dynamics & Nuclear Astrophysics**
- **Phases of Nuclear Matter**
- **Transport Phenomena & Phases of Nuclear Matter**
- **Reaction Dynamics**
- **Particle Production**
- **Studies of QCD Matter**
- **The Future & New Facilities**

NUCLEIC ACIDS
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 4-9, 2006
STEPHEN KOWALCZYKOWSKI &
SCOTT STROBEL, CO-CHAIRS
CYNTHIA BURROWS &
JODY PUGLISI, CO-VICE CHAIRS

- **Keynote Lecture**
  (Phil Sharp)
- **RNA Interference**
  (*Phil Sharp* / Narry Kim / Qinghua Liu)
- **Chromatin and Regulation**
  (*Bob Kingston* / Tom Owen-Hughes / Danesh Moazed / Michelle Wang)
- **Translation**
  (*Harry Noller* / Rachel Green / Jamie Cate / Olke Uhlenbeck)
- **Nucleic Acid Dynamics**
  (*Anna Pyle* / Taekjip Ha / Paul Rothemund / Marty Fedor)
- **Genome Structure and Maintenance**
  (*Roland Kanaar* / Ian Hickson / Tatsuya Hirano / Leonard Guarente)
- **Transcription**
  (*Bob Landick* / Terence Strick / Robert Singer / Steve Buratowski)
- **Ribozymes and Riboswitches**
  (*Tina Henkin* / Betsy Goodwin / Joseph Piccirilli / Dinsha Patel)
- **DNA Replication, Recombination and Repair**
  (*Virginia Zakian* / Paul Modrich / John Tainer / Steve Benkovic)

ORGANIC GEOCHEMISTRY
HOLDERNESS SCHOOL
PLYMOUTH, NH
AUG 6-11, 2006
STEVE LARTER, CHAIR
KATHERINE FREEMAN, VICE CHAIR

- **The Base of the Deep Crustal Biosphere and the Biogenic / Thermogenic Interface**
  (*John Parkes* / Brian Horsfield / Art Spivack)
- **The Interplay of Nature and Industry: Halogenated Organic Compounds in the Environment**
  (*Chris Reddy* / Emma Teuten / Heather Stapleton / Sheryl Tittlemier)
- **Molecular Signatures of Archaea and Archaeal Processes**
  (*Stuart Wakeham* / Christopher Francis / Samantha Joye / Andreas Gattinger)
- **Soil Organic Carbon and Climate**
  (*Gabriel Bowen* / *Thomas Wagner* / David Beerling / David Manning / Peter Raymond)
- **Hot Topics in Energy and Natural Resource Related Organic Geochemistry**
  (*Francois Behar* / presentations chosen from poster abstracts)
- **Hydrogen in the Biogeosphere**
  (*Alex Sessions* / David Valentine / Arndt Schimmelmann / Barbara Sherwood Lollar)
- **From Exploration to the Unconventional-Petroleum Geochemistry in the 21st Century**
  (*Artur Stankiewicz* / Erdem Idiz / Cliff Walters / Ian Head)
- **Hot Topics in Biogeochemistry**
  (*Kai Hinrichs* / presentations chosen from poster abstracts)
- **Computational Chemical Advances and Applications to Petroleum Geochemistry**
  (*Francois Lorant* / Elodie Salmon / Adri van Duin)

ORGANIC REACTIONS & PROCESSES
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 16-21, 2006
MATT MCINTOSH, CHAIR
JOS BRANDS, VICE CHAIR

- **Natural Products Synthesis 1**
  (*Rick Danheiser* / Lawrence Williams / Armen Zakarian / Steven Weinreb)
- **New Synthetic Methods 1**
  (*Tarek Sammakia* / Greg Dudley / Jeffrey Bode / Karl Scheidt)
- **Organometallics in Synthesis 1**
  (*Rick Bunt* / Christina White / Janis Louie / Daesung Lee)
- **Topics in Process Research 1**
  (*Art Harms* / Hannah Yu)
- **New Synthetic Methods 2**
  (*Frank McDonald*/ Rai-Shung Liu / Alison Frontier / Paolo Crotti)
- **Natural Products Synthesis 2**
  (*Jean Suffert* / Mike Harmata / Bob Grossman / Dan Romo)
- **Organometallics: Synthesis & Mechanisms**
  (*Peter Wipf* / David Vicic / Laurel Schafer / John Hartwig)
- **Biorganic & Related Topics**
  (Babak Borhan / Paul Carlier / John Porco)
- **Organometallics in Synthesis 2**
  (*Frank McDonald* / Jean-Luc Montchamp / Helen Lebel)
- **Topics in Process Research 2**
  (*Cecile Savarin* / Dave Hill)
- **New Synthetic Methods 3**
  (*Mukund Sibi* / Ohyun Kwon / Andreas Gansäuer / Guigen Li / Peter Somfai)
- **Organometallics in Synthesis 3**
  (*Lisa McElwee-White* / Jean-Luc Montchamp / Sherry Chemler)
- **Poster Competition & Featured Speaker**
  (*Scott Sieburth* / Rich Palmer)

ORGANOMETALLIC CHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 9-14, 2006
GERARD PARKIN, CHAIR
NORA RADU, VICE CHAIR

- **Opening Session**
  (*Nora Radu* / Maurice Brookhart / Russ Hughes)
- **Physical Methods and Techniques**
  (*Robert Bergman* / Graham Ball / Lilly Ackerman / Christophe Coperet / William Geiger)
- **Novel Reactivity and Transformations I**
  (*Karen Goldberg* / Richard Andersen / Philip Power / Geoff Cloke)
- **Applications to Organic Synthesis I**
  (*Dan Vanderlende* / Melanie Sanford / Antonio Togni / Patrick Lam)
- **Mechanistic & Theoretical**
  (*John Walzer* / Alan Goldman / Jack Norton / Mookie Baik)
- **Organometallics in Materials Chemistry and Biology**
  (*Roberto Sanchez Delgado* / Mark Thompson / Norman Herron / Charles Riordan)
- **Novel Reactivity and Transformations II**
  (*Sylviane Sabo-Etienne* / Dean Roddick / Poly Arnold / Oleg Ozerov)
- **Applications to Organic Synthesis II**
  (*Mao Minoura* / Laurel Schafer / Yann Schrodi / Rab Mulvey)
- **Back-to-the-Future**
  (*William Jones* / John Bercaw / Richard Schrock)

ORIGIN OF LIFE
BATES COLLEGE
LEWISTON, ME
JUL 23-28, 2006
JANET SIEFERT, CHAIR
ROBERT HAZEN, VICE CHAIR

- **Early Earth**
  (Ariel Anbar / Everett Shock / Paul Fawlkoski)
- **Prebiotic Chemistry**
  (Heather Bean / Martin Schoonen / Jeff Bada / Ram Krishnamurthy / Ernesto Di Mauro)
- **First Cells**
  (Martin Hanzcyc / Jack Szostak / Bill Martin / David Deamer / Andrew Pohorill)
- **First Cells, the Rock Record**
  (Roger Buick / Roger Summons / Joachim Brock)
- **Evolution of Information Systems**
  (George Fox / Kao C.C.)
- **Early Metabolisms**
  (Simonetta Gribaldo / Arturo Becerra / Purification Lopez-Garcia / Antonio Lazcano)
- **Atmospheric Evolution**
  (David Catlin / Jim Kasting)
- **Other Worlds**
  (Alison Alcott)
- **Life Census on Earth**
  (Maia Larios-Sanz / Forest Rohwer / Jim Elser)

GORDON-KENAN GRADUATE RESEARCH SEMINAR: ORIGIN OF LIFE
BATES COLLEGE
LEWISTON, ME
JUL 21-23, 2006
HEATHER BEAN, JANET SIEFERT &
NICOLLE ZELLNER, CO-CHAIRS
ARTURO BECERRA &
LUIS DELAYE, CO-VICE CHAIRS

- **Early Earth Environments**
  (Matthew Pasek / Feng Tian / Nicole Posth)
- **The Chemistry Leading to Life**
  (Irena Mamajanov / Qing Wang)
- **Early Microbial Evolution**
  (Gregory Fournier / Aubrey Zerkle / Andrew Czaja)

OSCILLATIONS & DYNAMIC INSTABILITIES IN CHEMICAL SYSTEMS
THE QUEEN'S COLLEGE
OXFORD, UK
JUL 30-AUG 4, 2006
PATRICK DE KEPPER, CHAIR
ANNE DE WIT, VICE CHAIR

- **Dynamic and Pattern Bifurcation Theory**
  (*Yasumasa Nishiura* / Takao Ohta / Thomas Erneux)
- **Nonequilibrium Biomimetic Systems**
  (*Irving Epstein* / George Whitesides / Kenichi Yoshikawa / Kenneth Showalter)
- **Application of Nonlinear Chemical Dynamics to Material Science**
  (*Pierre Borckmans* / Bartosz Grzybowski / Alexander Mikhailov)
- **Selected Abstracts for Oral Presentation I**
  (*Anne De Wit*)

- **Updates in Design and Use of Oscillatory Reactions**
  (*Steve Scott* / Miklos Orban / Friedrich Simmel / Tom Solomon)
- **Heterogeneous Patterning Systems**
  (*Rabih Sultan* / Istvan Lagzi / Daishin Ueyama / Oliver Steinbock)
- **Electrochemical Instabilities and Patterns**
  (*Vilmos Gaspar*/ Katharina Krischer / John Hudson)
- **Biological Systems**
  (*Preben Sorensen* / Fazoil Ataullakhanov / Jean-Christophe Leloup / Ewa Paluch)
- **Selected Abstracts for Oral Presentation II**
  (*Hana Sevcikova*)

PERMEABLE SEDIMENTS
COLBY COLLEGE
WATERVILLE, ME
JUN 25-30, 2006
CAROLYN OLDHAM &
TIMOTHY SHAW, CO-CHAIRS
MATTHEW CHARETTE &
MARKUS HUETTEL, CO-VICE CHAIRS

- **How Far Have We Come in Permeable Sediment Studies?**
  (*Richard Jahnke* / Richard Jahnke)
- **Material Transport and Alteration in Biocatalytic Reactors (Where Biology Meets Physics)**
  (*Charlie Paull* / Joel Koska / John Crusius)
- **Larger Scope and Scale of Permeable Systems (The Hydrogeology)**
  (*Andrew Boulton* / Alicia Wilson / Jeff McDonnell)
- **Biogeochemistry of Permeable Systems (Where Biology Meets Chemistry)**
  (*Joel Koska* / Kevin Kroeger / Steve Fries)
- **Case Studies (Sands and Beyond)**
  (*Markus Huettel* / Charlie Paull / Craig Glenn)
- **Whats New?**
  (State of the Art Methods and Models)
  (*Dirk De Beer* / Martiel Tallifert / Frank Wenzhöfer / Bayani R. Cardenas)
- **Response of Permeable Systems to Episodic Forcing**
  (*Carolyn Oldham*)
- **Case Studies**
  (Crossing Disciplinary Boundaries)
  (*Matt Charette* / Alicia Loveless / Dirk De Beer / Andrew Boulton)
- **Where Do We Go From Here?**
  (Summary and Outlook)
  (*Timothy Shaw* / Markus Huettel)

PHOSPHORYLATION & G-PROTEIN MEDIATED SIGNALING NETWORKS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 11-16, 2006
NATALIE AHN & BEVERLY ERREDE, CO-CHAIRS
HENRIK DOHLMAN &
JOANN TREJO, CO-VICE CHAIRS

- **Keynote Talks: Chemical-Genetic Approaches to Signal Transduction**
  (*Natalie Ahn* / Roger Tsien / Kevan Shokat)
- **Dynamics of Cell Signaling I**
  (*Melanie Cobb* / Barbara Graves / Susan Taylor / John Hancock / Richard Carthew)
- **New Technologies for Signaling Research**
  (*Douglas Lauffenburger* / Erin O'Shea / Roland Annan)
- **Developmental and Disease Signaling Pathways**
  (*Jeff Wrana* / Xi He / Joan Massague / Xuedong Liu / Frank Slack)
- **Mechanisms of Host-Pathogen Interactions**
  (*Kim Orth* / Jack Dixon / Daniel Kalman / J. Silvio Gutkind)
- **Dynamics of Cell Signaling II**
  (*Jean Wang* / Alexandra Newton / JoAnn Trejo / Henrik Dohlman / Michael Yaffe)
- **Cell Polarity and Morphogenesis**
  (*Jeremy Thorner* / Fred Chang / Richard Firtel)
- **Metabolic and Nutrient Sensing**
  (*Kun-Liang Guan* / Anne Brunet / Ben Neel / Gerald Shulman / Marian Carlson)
- **Stress and Disease**
  (*Gary Johnson* / Roger Davis / Zhijian James Chen)

PHOTONUCLEAR REACTIONS
TILTON SCHOOL
TILTON, NH
JUL 30-AUG 4, 2006
ADAM SARTY, CHAIR
REINHARD BECK &
SABINE JESCHONNEK, CO-VICE CHAIRS

- **Generalized Parton Distributions and Compton Scattering**
  (Barbara Pasquini / Harald Merkel / Frank Sabatie / Lennart Isaksson)
- **Nucleon Spin Structure**
  (Friedrich Klein / Paolo Pedroni / Nilanga Liyanage)
- **Parity Violation in Electron Scattering**
  (Barry Holstein / Frank Maas)
- **Baryon Spectroscopy**
  (*Larry Cardman* / T.S. "Harry" Lee / John Annand / Vladimir Pascalutsa)
- **Form Factors**
  (Garth Huber / Ashot Gasparian / Michael Kohl)
- **Studies of Few Nucleon Systems**
  (Steffen Strauch / P. von Neumann-Cosel / Volker Metag)
- **Advances in Theory**
  (Scott Bogner / Evengy Epelbaum / Winston Roberts)
- **Pushing the Envelope**
  (Peter Markowitz / Bradley Fillipone / Dipangkar Dutta / Rolf Ent)
- **Branching Out: Non-Traditional Applications**
  (William Bertozzi / Robert Lourie)

PHOTOSYNTHESIS
BRYANT UNIVERSITY
SMITHFIELD, RI
JUL 2-7, 2006
R. DAVID BRITT, CHAIR
WIM F.J. VERMAAS, VICE CHAIR

- **Photosynthesis and the Evolution of the Biosphere**
  (*Roger Summons* / Joe Kirschvink / David Catling / Mike Tice)
- **PSII and the OEC: Structural Studies**
  (Jan Kern / Jim Barber / Vittal Yachandra / Lou Noodleman)
- **PSII and the OEC: S-State Spectroscopy**
  (*Bridgette Barry* / Holger Dau / Taka-Aki Ono)
- **Antenna and Energy Transfer**
  (Rienk van Grondelle / Graham Fleming / Marloes Groot)
- **Energy and Electrons**
  (Alfred Holzwarth / Elmars Krausz / Oleg Poluektov)
- **Electrons and Protons**
  (Marilyn Gunner / Klaus Gerwert)
- **Other Biological Photosystems**
  (Janos Lanyi)
- **Photosynthesis and the Future of Solar Energy and Hydrogen Production**
  (Michael Seibert)
- **Broad Perspectives /**
  Young Investigators Session
  (Bob Blankenship)

PHYSICAL METALLURGY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 23-28, 2006
ALEX KING, DOUGLAS MEDLIN &
EUGEN RABKIN, CO-CHAIRS
JOHN ALLISON, HAMISH FRASER &
KEVIN HEMKER, CO-VICE CHAIRS

- **Grain Growth and Boundary Migration**
  (Lasar Shvindlerman / David Srolovitz)
- **Recrystallization and Texture Evolution**
  (Soeren Schmidt / Tony Rollett / Elizabeth Holm)
- **Materials Dynamics**
  (A.G. Yodh / Geoffrey Campbell / Ian Robertson)
- **Diffusion**
  (M.A. Dayananda / David Sholl / Hiroshi Numakura)
- **Interfacial Processes**
  (Yuri Mishin / Mike Finnis / Sadahiro Tsurekawa)
- **Precipitation and Coarsening**
  (David Seidman / Alan Ardell / Long-Qing Chen / Chris Wolverton / Emmanuelle Marquis)
- **Wetting/Liquid-Solid Interface**
  (Dominique Chatain / Tony Tomsia / Mark Asta)

PHYSICS RESEARCH AND EDUCATION: ELECTROMAGNETISM
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 11-16, 2006
KERRY BROWNE &
STAMATIS VOKOS, CO-CHAIRS
BRADLEY AMBROSE &
WOLFGANG CHRISTIAN, CO-VICE CHAIRS

- **Opening Session**
  (*Robert Hilborn* / David Griffiths / Bill Dorland)
- **Historical Underpinnings of Electricity and Magnetism**
  (*E.F. (Joe) Redish* / Daniel Siegel / Robert Morse)
- **Curricular Approaches to Electricity and Magnetism**
  (*Thomas Moore* / Ruth Chabay & Bruce Sherwood / Bruce Patton / Igal Galili)
- **Physics Education Research in Electricity and Magnetism**
  (*David Maloney* / Peter Shaffer / Robert Beichner / Stephen Kanim)

- **Theoretical and Mathematical Challenges to Learning Electricity and Magnetism**
(*Chandralekha Singh* / Rachel Scherr / Corinne Manogue)
- **Applications of Electromagnetism in Modern Optics Research**
(*Charles Holbrow* / Gabriel Spalding / Enrique (Kiko) Galvez)
- **Computer Simulations for Teaching Optics and Electromagnetism**
(*Wolfgang Christian* / John Belcher / John Foley)
- **Applications of Electromagnetism in Atmospheric and Astrophysical Research**
(*Kristina Lynch* / Phil Krider / Ramon Lopez / Michael Brown)
- **Applications of Electromagnetism in Biological and Materials Science Research**
(*Raymond Goldstein* / Brent Hoffmeister / Laura Clarke)

PLANT & FUNGAL CYTOSKELETON
PROCTOR ACADEMY
ANDOVER, NH
AUG 20-25, 2006
ANTHONY BRETSCHER, CHAIR
SUSAN DUTCHER, VICE CHAIR

- **Establishment and Maintenance of Polarity**
(*Gerd Jurgens* / Sheila McCormick / Mark Rose / Ken Sawin / Laurie Smith)
- **Regulation and Assembly of Cytoskeletal Structures: Microtubules**
(*Richard Cyr* / Jacek Gaertig / Geoff Wasteneys)
- **Regulation and Assembly of Cytoskeletal Structures: Microfilaments**
(*Chris Staiger* / Bruce Goode / Alice Cheung / Patrick Hussey)
- **Mechanisms and Fidelity in Cell Division: Mitosis**
(*Kerry Bloom* / Tomoyuki Tanaka / David Pellman)
- **Mechanisms and Fidelity in Cell Division: Organelle Segregation and Cytokinesis**
(*Rong Li* / Arturo de Lozanne / Tom Pollard / Liza Pon / Lois Weisman)
- **Genomic Approaches**
(*Charles Boone* / Magdalena Bezanilla)
- **Membrane Traffic and the Cytoskeleton**
(*Brenda Andrews* / Federica Brandizzi / Patrick Brennwald / Doug Cole / Erik Nielson)
- **Regulation and Coordination of the Cytoskeleton**
(*Lynne Quarmby* / Dominique Bergmann / David Drubin / Kathy Gould / Frank Luca)

PLANT CELL WALLS
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 30-AUG 4, 2006
NICHOLAS CARPITA, CHAIR
DEBRA MOHNEN, VICE CHAIR

- **Opening Keynote Lecture**
(*Keith Roberts*)
- **Evolution of the Cell Wall**
(*Alison Roberts* / William York / Malcolm O'Neill / Marcos Buckeridge)
- **Polysaccharide Structure and Architecture**
(*Fons Voragen* / Henk Schols / John Brady)
- **Plant Cell Walls in Plant-Microbe Interactions**
(*Shauna Somerville* / Joss Rose)
- **Biosynthesis I**
(*Ken Keegstra* / Wolf-Dieter Reiter)
- **Biosynthesis II**
(*Kanwarpal Dhugga* / Vincent Bulone / Geoff Fincher / Mick Held)
- **Biosynthesis III**
(*Chris Somerville* / Simon Turner)
- **Growth and Development I**
(*Dan Cosgrove* / Janet Braam)
- **Growth and Development II**
(*Maureen McCann* / Markus Pauly)
- **Wood Formation**
(*Tuula Teeri* / Zheng-Hua Ye)
- **New Technologies in Glycobiology**
(*Michael Hahn* / Richard Alvarez / Harry Brumer)
- **Biomedical Uses of Cell-Wall Polysaccharides**
(*Peter Ulvskov* / Debra Mohnen / Haruki Yamada / Yan Chang / Marco Morra)
- **Closing Keynote Lecture**
(L. Andrew Staehelin)

PLANT MOLECULAR BIOLOGY
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 16-21, 2006
SHEILA MCCORMICK, CHAIR
RICHARD AMASINO, VICE CHAIR

- **Light Perception**
(*Rick Amasino* / Natan Nelson / Rick Vierstra / Kevin Folta)
- **Metabolic Signaling**
(*Harry Klee* / Carol Mackintosh / Yair Shachar-Hill / Moto Ashikari / Toni Kutchan)
- **Cellular Sensing**
(*Sandy Lazarowitz* / Simon Gilroy / Dave Ehrhardt / Alice Cheung)
- **Hormonal Signaling Pathways**
(*Simon Gilroy* / Mark Estelle / Jonathan Jones / Miyako Ueguchi-Tanaka / Harry Klee)
- **Intracellular Dynamics**
(*Dave Ehrhardt* / Laurie Smith / Sandy Lazarowitz / Kelly Dawe)
- **Plant Defense Systems**
(*Jonathan Jones* / Jeff Dangl / Thomas Boller / Ian Baldwin / Mary Beth Mudgett)
- **Keynote Lecture**
(Jim Carrington)
- **Developmental Transitions**
(*Laurie Smith* / Miltos Tsiantis / Rick Amasino / Xuemei Chen / Doris Wagner)
- **Epigenetic Regulation of Gene Expression**
(*Xuemei Chen* / Steve Jacobsen / Damon Lisch / Jeff Chen)

PLASMA PROCESSING SCIENCE
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUL 16-21, 2006
ALEXANDER FRIDMAN, CHAIR
JEAN-MICHEL POUVESLE, VICE CHAIR

- **Plasma Light Sources**
(*Jean-Michel Pouvesle* / Hae June Lee / M. Haverlog)
- **Plasma in Biology and Medicine**
(*Alexander Fridman* / A. Ohl / Awakowicz / Mounir Laroussi)
- **Plasma in Hydrogen Production, Fuel Cells, Materials Treatment**
(*Francois Gitzhofer* / Pascal Brault / Lesli Bromberg)
- **Microplasmas: Physics and Applications**
(*Marc Kushner* / Kunhide Tachibana / Lax Raja / Jeffrey Hopwood)
- **Atmospheric Pressure Plasma Chemistry**
(*Joachim Heberlein* / Armelle Vardelle / Alexander Gutsol)
- **Plasma in Micro- and Nano- Technologies**
(*Richard van de Sanden* / Shiritani / Fred Roozenboom / David Blank)
- **Architectures of Reactors for Plasma Modification of Polymers**
(*Riccardo d'Agostino* / Jorg Winter / Michael Barns / Uwe Kortshagen)
- **Nano-Particles and Nano-Structure Sin Plasma**
(*Steven Girshick* / Michel Wertheimer / E. Aldea / Naima Boutroy)
- **Aerodynamics and Plasma Aided Combustion**
(*Bish Ganguly* / Sergey Macheret / Richard Engeln)

PLASMONICS
KEENE STATE COLLEGE
KEENE, NH
JUL 23-28, 2006
ALBERT POLMAN, CHAIR
HARRY ATWATER, VICE CHAIR

- **Plasmonic Meta-Materials**
(*Nader Engheta* / Eli Yablonovitch / David R. Smith)
- **Planar Surface Plasmon Polariton Structures**
(*Alain Dereux* / Sergey Bolzhevolnyi / Jean-Claude Weeber / Mark Brongersma / Han Woerdman)
- **Plasmonic Nanostructures I**
(*David A.B. Miller* / Naomi Halas / Amanda Haes / Peter Nordlander)
- **Plasmonic Nanostructures II**
(*Fritz Keilmann* / Mark Stockman / Younan Xia / Gary Wiederrecht / Paul Alivisatos)
- **THz Plasmons and Phonons**
(*Stefan Maier* / Gennady Shvets / Rainer Hillenbrand)
- **Active Plasmonic Structures and Devices**
(*Jelena Vuckovic* / Satoshi Kawata / Federico Capasso / Axel Scherer / Teri Odom / Marin Soljacic)
- **Ultramicroscopy**
(*Pieter Kik* / Xiang Zhang / Kobus Kuipers / Vahid Sandoghdar / Vladimir Shalaev)
- **Plasmonic Nanostructures III: Holes and Arrays**
(*William Barnes* / Thomas Ebbesen / Henri Lezec / Francisco Garcia Vidal / Javier Garcia de Abajo)
- **Frontiers of Plasmonics**
(*Harry Atwater*)

POLYMER PHYSICS
CONNECTICUT COLLEGE
NEW LONDON, CT
JUL 23-28, 2006
FRANK BATES, CHAIR
JANE LIPSON, VICE CHAIR

- **Biological and Medical Implications**
(Dan Hammer / Ka Yee Lee / Ron Larson)

- **Surfaces and Thin Films**
  (*Karen Winey* / Rick Register /
  Steve Granick / Paul Nealey / Jan Genzer)
- **Electronic and Optical Implications**
  (Henning Sirringhaus /
  Eugenia Kumacheva / John Rogers /
  Mike Rubner / George Hadziouannou)
- **Self and Directed Assembly**
  (*Steve Hahn* / Wes Burghardt /
  Stephan Förster / Rachel Segalman /
  Uli Weisner / Nitash Balsara)
- **Theoretical Considerations**
  (*Scott Milner* / Jane Lipson / Dave Morse /
  Venkat Ganesan / Doros Theodoros)

POST-TRANSCRIPTIONAL GENE REGULATION, THE BIOLOGY OF
THE QUEEN'S COLLEGE
OXFORD, UK
AUG 13-18, 2006
JANE WU, CHAIR
ADRIAN KRAINER, VICE CHAIR

- **System Biology Approaches to RNA Processing**
  (Jason Johnson / Jack Keene / Don Rio /
  William Marzluff / Ben Blencowe)
- **Pre-mRNA Splicing: Splicing Factors, Mechanisms & Human Diseases**
  (Reinhard Luhrmann / S.C. Cheng /
  Magda Konarska / Jon Staley / W.Y. Tarn /
  Tom Misteli / Gideon Dreyfuss)
- **Pre-mRNA Splicing & Cancer**
  (X.D. Fu / Adrian Krainer / Benoit Chabot /
  Mariano Garcia-Blanco / Robert Darnell)
- **Alternative Splicing & its Regulation**
  (Tim Nilsen / Kristen Lynch / Jim Bruzik /
  Chris Smith / Maurice Swanson /
  Doug Black / Tom Cooper)
- **Transcription, Splicing & the 3¹ End Formation**
  (Jim Manley / Michael Rosbash /
  Steve Buratowski / C. MacDonald /
  Joel Richter / David Brow)
- **Regulation of RNA Stability**
  (*Lynne Maquat* / Stuart Peltz /
  Christoph Moroni / Elmar Wahle /
  Jens Lykke-Andersen / Marvin Wickens)
- **Nuclear Transport and RNA Localization: RNAs & Proteins**
  (Melissa Moore / Susan Wente /
  Anne Ephrussi / Elisa Izaurralde /
  Robert Singer)
- **Evolution of Regulated RNA Processing & Complex Genes**
  (Brent Graveley / Tom Blumenthal /
  Angela Krämer / Jean Beggs / M. Ares /
  Paula Grabowski / Gil Ast / M.Y. Long)
- **Small RNA Genes and Other Breaking News in the RNA World**
  (Richard Carthew / Kathryn Barton /
  Alan Weiner / Masatoshi Hagiwara /
  Robin Reed)

POSTHARVEST PHYSIOLOGY
CONNECTICUT COLLEGE
NEW LONDON, CT
JUL 9-14, 2006
CHRISTOPHER WATKINS, CHAIR
ELIZABETH BALDWIN, VICE CHAIR

- **Setting the Scene**
  (*Don Grierson* / Elizabeth Baldwin /
  Angelos Kanellis / William Laing)
- **Genetic Control of Ripening**
  (*Mondher Bouzayen* / Jim Giovannoni /
  Graham Seymour)
- **Ethylene and Ripening**
  (*Christian Chervin* / Yasutaka Kubo /
  Pietro Tonutti)
- **Fresh Cut Physiology**
  (*James Gorny* / John Beaulieu /
  M. Isabel Gil / Deidre Holcroft)
- **Cell Walls**
  (*John Labavitch* / Joss Rose / Robert Paull)
- **Flavor and Aroma**
  (*John Fellman* / Bart Nicoli /
  Harry Klee / David Clark)
- **Chilling**
  (*Susan Lurie* / Teresa Lafuente / Ron Porat)
- **Controlling Senescence**
  (*Ian Ferguson* / Susheng Gan /
  Amnon Lers / Michael Reid)
- **Commercial Postharvest Handling Systems**
  (*Adel Kader* / Andy Medlicott / Jeff Brecht)

PROPROTEIN PROCESSING, TRAFFICKING & SECRETION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 9-14, 2006
NABIL G. SEIDAH, CHAIR
RICHARD E. MAINS, VICE CHAIR

- **Structural Biology and Molecular Interactions**
  (*Wolfram Bode* / Manuel E. Than /
  Sean T. Prigge / Benjamin F. Cravatt /
  Christopher Overall)
- **Novel Developments in Processing Enzymes**
  (*Lloyd Fricker* / Donald F. Steiner /
  Majambu Mbikay / Annik Prat /
  Hugh Bennett / Niamh X. Cawley /
  Francois Jean / Robert Fuller)
- **Therapeutic Targets And Approaches**
  (*Iris Lindberg* / Nancy Thornberry /
  Richard J. Lewis / Illana Gozes /
  James A. Wells)
- **Implication of Processing Enzymes and Defective Processing in Physiology and Disease I**
  (*Richard E. Mains* / Alan Attie /
  William E. Balch / William C. Wetsel /
  Weijun Jin / Sushil K. Mahata /
  Melitta Schachner)
- **Implication of Processing Enzymes and Defective Processing in Physiology and Disease II**
  (*Zena Werb* / Susan Wray /
  Suneel S. Apte / Zena Werb)
- **Organelle Biogenesis, Cellular Trafficking and Novel Features of Secretory Compartments I**
  (*Gary Thomas* / Hugo J. Bellen /
  Hans-Hermann Gerdes /
  Shawn M. Ferguson / Gerrit Van Meer)
- **Organelle Biogenesis, Cellular Trafficking and Novel Features of Secretory Compartments II**
  (*Tim Reudelhuber* / Y. Peng Loh /
  Duanginq Pei / Priscilla S. Dannies)
- **Emerging Functions of Processing Enzymes of Sequenced Genomes**
  (*Michel Chrétien* / Charles S. Craik /
  Qingyu Wu)
- **Intramembrane Proteolysis and Cellular Function**
  (*Michael S. Wolfe* / Michael S. Wolfe /
  Raphael Kopan / Fréderick Checler /
  Mathew Freeman / Tim Clausen)
- **Proteases, Cellular Trafficking & Physiopathologies: The Next Generation**
  (*John Bergeron* / Khris Gevaert /
  John Creemers)

PROTEOGLYCANS
PROCTOR ACADEMY
ANDOVER, NH
JUL 9-14, 2006
ALAN RAPRAEGER, CHAIR
THOMAS WIGHT, VICE CHAIR

- **Late Breaking Developments**
  (*Alan Rapraeger*)
- **Biosynthesis and Structure of Glycosaminoglycans**
  (*Barbara Mulloy* / Lena Kjellén /
  Kazuyuki Sugahara / Julie Leary /
  Koji Kimata)
- **Structure-Activity of Glycosaminoglycans**
  (*Dina Ron* / John Gallagher /
  Moosa Mohammadi / Amanda Proudfoot)
- **Proteoglycans of the Musculoskeletal System**
  (*Renato Iozzo* / Marian Young /
  Lilliana Schaefer / Enrique Brandan /
  Winston Kao)
- **Proteoglycans in Cell Signaling Mechanisms**
  (*Anne Woods* / Pascale Zimmermann /
  Bradley Olwin / Eok-Soo Oh)
- **Proteoglycans in Development**
  (*Scott Selleck* / Rahul Warrior /
  Henry Roehl / Norman Rosenblum /
  Sara Olson)
- **Proteoglycans in Injury and Inflammation**
  (*Thomas Wight* / Burton Yang /
  Paul Noble / Anna Plaas)
- **Proteoglycans in Cancer**
  (*Ralph Sanderson* / Renato Iozzo /
  Steven Rosen / Lena Claesson-Welsh /
  Hiroyuki Aburatani)
- **Proteoglycans in Disease Models**
  (*Shukti Chakravarti* / Jeffrey Esko /
  Bryan Toole)

PROTEOLYTIC ENZYMES & THEIR INHIBITORS
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 2-7, 2006
ROY BLACK, CHAIR
JAN POTEMPA, VICE CHAIR

- **Developments in Imaging and Mass Spec Applications**
  (*Chris Overall* / Galia Blum /
  Peter Schulz-Knappe)
- **Proteases in Inflammation and Immunology**
  (*Phil Bird* / Sergio Trombetta /
  Nicolas Bidere / Christine Pham)
- **De-Ubiquitinating Enzymes**
  (*Keith Wilkinson* / Bob Cohen / Kim Orth)
- **New Insights into Specificity, Mechanism and Regulation**
  (*Guy Salvesen* / Ed Madison /
  Martin Lackmann / Wolfram Bode /
  Enrico Di Cera / James Huntington)
- **Proteases in Infectious Diseases**
  (*Rob Pike* / Jakki Cooney / Sin Urban /
  Po-Huang Liang)
- **New Developments in Protease Inhibition**
  (*Nancy Thornberry* / Daniel Bur /
  Dennis Yamashita / David Fairlie /
  Gary Silverman / Markus Gruetter)

- **Proteases in the Brain**
  (*Michael Wolfe* / Gang Yu / Pierluigi Nicotera)
- **New Roles of Proteases in Homeostasis and Repair**
  (*Bill Parks* / Christoph Peters / Dan Greenspan / Margarete Heck)

RADIATION CHEMISTRY
COLBY COLLEGE
WATERVILLE, ME
JUL 2-7, 2006
JOHN MILLER, CHAIR
DAVID BARTELS, VICE CHAIR

- **Nano and Interfaces**
  (*Piotr Ulan'ski* / Jacqueline Belloni / Jay LaVerne)
- **X-Rays, Electrons and Attoseconds**
  (*Marshall Newton* / Alexander Föehlisch / Jean-Marc Jung / Anders Nilsson)
- **Biology and Radiation**
  (*Chantal Houée-Lévin* / Elspeth Garman / Marianne Sowa)
- **Nano-Materials**
  (*Seiichi Tagawa* / Andy Monkman / John Warman / Shu Seki)
- **Young Investigators**
  (*David Bartels*)
- **Electrons and Electron Transfer**
  (*Benjamin Schwartz* / Mehran Mostafavi / Ilya Shkrob / Andrew Cook)
- **DNA and Radiation Biology**
  (*Diane Cabelli* / Robert Anderson / Betsy Sutherland)
- **Ions, Electrons and Supercritical Fluids**
  (*Yosuke Katsumura* / Vladimir Feldman / Mingzhang Lin / Jean-Philippe Renault)
- **Low Energy Electrons**
  (*James Wishart* / Leon Sanche / Greg Kimmel)

REPRODUCTIVE TRACT BIOLOGY
CONNECTICUT COLLEGE
NEW LONDON, CT
JUN 18-23, 2006
JAMES CROSS &
JEFFREY POLLARD, CO-CHAIRS
THOMAS SPENCER, VICE CHAIR

- **Keynote Lecture: Sex Determination**
  (Robin Lovell-Badge)
- **New Technologies**
  (Monica Justice)
- **Development of The Male and Female Reproductive Tract**
  (*Fuller W. Bazer* / Matt Hardy / David Sassoon / Gen Yamada / Robert Viger / Thomas Spencer)
- **Gonad and Accessory Gland Development**
  (*Geula Gibori* / Norman Hecht / Alexander Agoulnik / Barry Hinton / Kenneth McNatty)
- **Placentation**
  (*James L. Cross* / Michael Soares / Daniel Constam / John Kingdom / Hanna Mikkola / Jacqueline Wallace)
- **Reproductive Aging**
  (*Nanette Santoro* / Barry Zirkin / J. Lisa Tenover / Gerson Weiss)
- **Immune Influences on the Reproductive System**
  (*Joan Hunt* / Jane Salmon / Carole Mendelson / Mark Hedger / John Atkinson)
- **Hormone Action**
  (*Kenneth S. Korach* / Hiro Kiyokawa / Ellis Levin / Holly Ingraham)
- **Implantation**
  (*Susan Kimber* / Colin L. Stewart / Lois Salamonsen / Francesco DeMayo / John Rasweiler)
- **Keynote Address II**
  (Michael Roberts)

ROCK DEFORMATION
BIG SKY RESORT
BIG SKY, MT
SEP 3-8, 2006
MARK JESSELL, CHAIR
GREG HIRTH, VICE CHAIR

- **Temporal Periodicity of Geological Processes**
  (*Jean-Pierre Burg* / Tom Jordan / David Bercovici)
- **Seeing is Believing: Results from New In Situ Experiments**
  (*Renée Heilbronner* / Don Weidner / David Prior / Henning Friis Poulsen)
- **Poster Session 1**
  (*Greg Hirth*)
- **Complex Rheologies**
  (*Ernie Rutter* / Laurent Montesi / Marco Herwegh / Peter Vrojlik)
- **Dating Deformation**
  (*Gordon Lister* / Christian Teyssier / Olivier Vidal)
- **Geo-Materials Simulation**
  (*John Wheeler* / Paul Bons / Einat Aharonov / Andrea Tommasi)
- **Poster Session 2**
  (*Greg Hirth*)
- **Natural Laboratories**
  (*Dani Schmid* / Janos Urai / Marian Holness / Steve Hickman)
- **Single Crystal vs. Aggregate Behaviour**
  (*Yanbin Wang* / Jean-Pierre Gratier / Brian Evans)

SALT & WATER STRESS IN PLANTS
MAGDALEN COLLEGE
OXFORD, UK
SEP 3-8, 2006
DOROTEA BARTELS, CHAIR
JOHN CUSHMAN &
MARK TESTER, CO-VICE CHAIRS

- **Osmosening and Early Signalling**
  (*Erwin Grill* / Julian Schroeder / Janet Wood / Kazuko Yamaguchi-Shinozaki)
- **Stress Response Gene Expression**
  (*John Cushman* / Jian-Kang Zhu / Motoaki Seki / Montserrat Pages / Jeffrey Leung)
- **Cellular Responses to Salt and Water Stress**
  (*Rana Munns* / Mike Blatt / Alistair Hetherington / Yehoram Leshem)
- **Crosstalk Between Different Stress Pathways**
  (*Teun Munnik* / Ron Mittler / Csaba Koncz / Radhika Desikan / Peter McCourt)
- **Stress Protein and Protein Signature**
  (Alejandra Covarrubias / Mike Hasegawa / Bob Sharp)
- **Ion and Water Homeostasis**
  (*Mark Tester* / Eduardo Blumwald / Steve Tyerman / Jose Pardo / Ray Bressan)
- **Model Systems Adapted to Stress**
  (Jonathan Phillips / Jill Farrant / Mel Oliver)
- **Crop Production and Metabolite Analysis**
  (*Ruth Grene* / Ju-Kon Kim / Harkamal Walia / Ute Roessner-Tunali / Mathew Reynolds)
- **Biotechnology**
  (*Henry Nguyen* / Oliver Ratcliffe / Don Nelson / Ray Wu)

SCIENCE & TECHNOLOGY POLICY
BIG SKY RESORT
BIG SKY, MT
AUG 13-18, 2006
FRED GRINNELL & SKIP STILES, CO-CHAIRS
RACHEL ANKENY &
DAVID GUSTON, CO-VICE CHAIRS

- **What is Science and Technology Policy?**
  (Wil Lepkowski / Radford Byerly, Jr. / M.J. Finley Austin / Elisa Eiseman)
- **Science Policy Directions and Advice: Biotech vs. Nanotech**
  (*Michael Rodemeyer* / L. Val Giddings / Sharon Hays / Julia Moore / Greg Simon)
- **Scientific Workforce: Domestic and International Factors**
  (*Patty McAllister* / Heath Brown / Andrea Stith)
- **Assessing Biomedical Promise for Novel Diagnostics and Treatments**
  (*Susan M. Fitzpatrick* / Susan M. Fitzpatrick / Joseph Dumit / Donna Gerardi Riordan / H. Gilbert Welch)
- **Energy Policy: Change Agent or Implementation of the Status Quo**
  (*Jeff Warren* / Bryan Hannegan / Paul Komor / Daniel Metlay / Cindy Yeilding)
- **Schumpeter's Next Wave: Convergence of Nanotechnology, Biotechnology, Information Science and Cognitive Science**
  (*Braden Allenby* / Braden Allenby / Clint Andrews / Thomas H. Karas / Barbara Karn)
- **Impact of International Intellectual Property Law and Policy on Global Biotechnology and Health Care**
  (*Shobita Parthasarathy* / Shobita Parthasarathy / John Barton / Hannah Kettler)
- **Meta-Analysis of the Previous Six Sessions and Extended Group Discussion**
  (Donna J. Dean / Colin Macilwain / Daniel Sarewitz)
- **Decision Making in a World of Uncertainty**
  (*Roger A. Pielke, Jr.* / Roger Pielke / David H. Guston / Robert Lempert)

SENSORY CODING AND THE NATURAL ENVIRONMENT
BIG SKY RESORT
BIG SKY, MT
AUG 27-SEP 1, 2006
JACK GALLANT &
MICHAEL LEWICKI, CO-CHAIRS
MICHAEL BERRY &
EERO SIMONCELLI, CO-VICE CHAIRS

- **Keynote Lecture**
  (William Bialek)
- **Statistics and Computational Processing of Natural Signals**
  (*James Elder* / Michael Black / Pietro Perona / Antonio Torralba)

- **Biological Processing of Natural Sounds**
  (*Xiaoqin Wang* / Daniel Margoliash / Cory Miller / Robert Liu)
- **Biological processing of Natural Scenes: Early**
  (*Matteo Carandini* / Stephen Baccus / Vincent Bonin)
- **Biological processing of Natural Scenes: Late**
  (*James Mazer* / Benjamin Willmore / James DiCarlo)
- **Non-Stationarities, Adaptation and Learning**
  (*Adrienne Fairhall* / Garrett Stanley / David Kleinfeld)
- **Generation and Sensation of Dynamic Signals**
  (*Mitra Hartmann* / Mimi Koehl / Maurice Chacron)
- **Natural Signal Perception in Humans**
  (*David Tolhurst* / Laurent Itti / Hugh Wilson)

SIGNAL TRANSDUCTION BY ENGINEERED EXTRACELLULAR MATRICES
CONNECTICUT COLLEGE
NEW LONDON, CT
JUL 2-7, 2006
MICHAEL SHEETZ, CHAIR
MOLLY SHOICHET, VICE CHAIR

- **Systems Engineering of Cell Growth**
  (*Michael Sheetz* / Joan Brugge / Anand Asthagiri / Ken Yamada)
- **Cellular Assembly of Matrices**
  (Fred Keeley / Robert Mecham / Jean Schwartzbauer / Fred Grinnell)
- **Engineering Cells and Matrices for Function**
  (*Mo Heidaran* / Andres Garcia / Linda Griffith / Jennifer West)
- **Cellular NanoResponses**
  (*Don Bottaro* / Bob Campenot / Dan Fletcher / Wa Chiu)
- **Nanoengineering of Matrices for Cell Function**
  (Benny Geiger / Chris Chen / Christopher Ober)
- **Cellular Signaling from Matrices, Hormones or Growth Factors**
  (*David Mooney* / David Letourneau / Paul Janmey / Rene Marc Mege)
- **Engineering Cell Responses to ECM, Hormones or Growth Factors**
  (*Viola Vogel* / *Patrick Slayton* / Lonnie Shea / Dan Hammer)
- **Regeneration and Wound Healing**
  (*Eleni Kousvelaril* / Jay Groves / Sam Weiss / Gary Levy / Malcolm Snead)
- **Engineering Tissue Function**
  (*Helen Lu* / Alyssa Panitch / Jonathan Mansbridge / Molly Shoichet)

SIGNALING BY ADHESION RECEPTORS
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MA
JUN 25-30, 2006
JOAN BRUGGE, CHAIR
W. JAMES NELSON, VICE CHAIR

- **Keynote Address**
  (Alan Hall)
- **Cadherins and Protocadherins in Development**
  (Rolf Kemler / Tom Clandinin)
- **Cell Migration**
  (Rick Horwitz / John Condeelis / Frank Gertier)
- **Cytoskeletal Dynamics**
  (Clare Waterman-Storer / Inke Nathke / Benny Geiger / Art Alberts)
- **Cell Polarity**
  (Ian Macara / Mark Peifer / Helen McNeill / Kozo Kaibuchi)
- **Cell-Cell Adhesion**
  (James Nelson / Shoichiro Tsukita / Lawrence Holzman / Kathy Green)
- **Cell Matrix Signaling**
  (Nick Brown / Anthony Koleske / Jim Norman / Patricia Keely)
- **Mechanotransduction**
  (Chris Chen / Mike Sheetz / Martin Schwartz / Valerie Weaver)
- **Development and Differentiation**
  (Elaine Fuchs / Fiona Watt / Alexandra Schambony)
- **Regulation of Cell Adhesion**
  (Mark Ginsberg / Nancy Hogg / Judith White)

SINGLE MOLECULE APPROACHES TO BIOLOGY
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUN 18-23, 2006
LORI GOLDNER & SUNNEY XIE, CO-CHAIRS
TAEKJIP HA &
XIAOWEI ZHUANG, CO-VICE CHAIRS

- **Single Molecule Approaches: Coming of Age**
  (*Taekjip Ha* / Steven Chu / W.E. Moerner / Steven Block)
- **Nucleic Acid Enzymes**
  (*Steven C. Harrison* / David Bensimon / Steve Kowalczykowski / Nynke Dekker / David Lilley)
- **Methodology I**
  (*Michel Orrit* / Shimon Weiss / Petra Schwille / Stefan Hell)
- **Molecular and Cellular Mechanics**
  (*Helen Hansma* / Michael Sheetz / Julio Fernandez / Klaus Schulten / Michelle Wang)
- **RNA**
  (*Ignacio Tinoco* / Dan Herschlag / Sarah Woodson / Nils Walter)
- **Methodology II**
  (*Rudolf Rigler* / Charles Lieber / Stephen Quake / Owe Orwar / John J. Kasianowicz)
- **Molecular Motors**
  (*David Warshaw* / Toshio Yanagida / Paul Selvin / Richard Berry)
- **Live Cell Imaging**
  (*Peter Devreotes* / Watt Webb / Atsushi Miyawaki / Jennifer Lippincott-Schwartz)
- **Single Molecule Approaches: In the Future**
  (*Xiaowei Zhuang* / Carlos Bustamante / Robert Singer / Jim Spudich)

SOLID STATE CHEMISTRY I
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 23-28, 2006
TERRELL VANDERAH, CHAIR
MERCOURI KANATZIDIS, VICE CHAIR

- **Length-Scale Problems**
  (*Ram Seshadri* / *Michael Lufaso* / Simon Billinge / Pierre Bordet / Yuri Grin / Paul Maggard)
- **Solid State Chemistry on the Local Scale**
  (*Bob Roth* / *Theo Siegrist* / Ian Grey / Ray Withers)
- **Nanoscale Materials Chemistry**
  (*Stephanie Brock* / *James Martin* / Ray Schaak / Kyoung-Shin Choi / Debra Rolison)
- **Ions in Motion, and Superspace**
  (*Sossina Haile* / *Clare Grey* / Mike Thackeray / Bernie Wuensch / Jacques Darriet)
- **Dielectric Materials Chemistry**
  (*Gustav VonTendaloo* / *Patrick Woodward* / Igor Levin / Susanne Stemmer)
- **Electronic Solids**
  (*Bob Cava* / *Michael Hayward* / Paul Attfield / Ian Fisher / Martin Jansen / Elizabeth Dickey)
- **Theoretical/Computational Approaches**
  (*Maggie Geselbracht* / *Charlie Torardi* / Nicola Spaldin / Tim Hughbanks)
- **Frameworks and Non-Oxide Materials**
  (*Nate Brese* / *Ed Gillan* / Matt Rosseinsky / David Mitzi / Simon Clarke / Amparo Fuertes)
- **An Extraterrestial View**
  (*Steve Keller* / Dean Eppler)

STEREOCHEMISTRY
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUN 18-23, 2006
ERICK CARREIRA, CHAIR
CHRIS SENANAYAKE, VICE CHAIR

- **New Reagents and Catalysts**
  (*Karl Scheidt* / Scott Denmark / Gregory Fu)
- **Novel Strategies**
  (*Doug Frantz* / André Charette / Karl Scheidt / Justin Du Bois)
- **Stereoselective Synthesis**
  (*Joseph Fox* / Rene Peters / Viresh Rawal)
- **Biology & Chemistry**
  (*Jay Siegel* / Samuel Gellman / Karl Gademann / Ana Mapp)
- **Chemistry & Biology**
  (*Karl Gademann* / Eric Sorensen / Steven Benner)
- **Novel Methodology**
  (*Rene Peters* / Todd Jones / Doug Frantz / Hélène Lebel / John Hartwig)
- **Methodological Advances**
  (*Hélène Lebel* / Joelle Prunet / Andre Yudin / Scott Miller)
- **Applications of Catalysis**
  (*Andre Yudin* / Vittorio Farina / Joseph Fox / Janine Cossy)
- **Synthesis & Catalysis**
  (*Joelle Prunet* / Shu Kobayashi / David Evans)

SYNAPTIC TRANSMISSION
COLBY-SAWYER COLLEGE
NEW LONDON, NH
JUL 23-28, 2006
JULIE KAUER, CHAIR
RALF SCHNEGGENBURGER, VICE CHAIR

- **Keynote Lectures**
  (Thomas Sudhof / Roberto Malinow)
- **Transmitter Release Mechanisms I**
  (David Zenisek / Tomoyuki Takahashi / Takeshi Sakaba / Ege Kavalali)
- **Dendritic Signals**
  (Michael Ehlers / Robert Malenka / Kelsey Martin)
- **Synaptic Control of Neural Circuits**
  (Bernardo Sabatini / Gilles Laurent / Jeff Isaacson / Catherine Woolley / Lori McMahon)
- **Transmitter Release Mechanisms II**
  (Isabel Llano / Ling Gang Wu / Sandra Bajjalieh)
- **Synaptic Plasticity**
  (Roger Nicoll / Dan Madison / Haruo Kasai / Chris McBain)
- **Developmental Plasticity**
  (Marla Feller / Kimberley McAllister / Mark Bear)
- **Novel Synaptic Mechanisms**
  (Pierre-Marie Lledo / Gary Westbrook / Josef Bischofberger / Elizabeth Jonas / Dwight Bergles)
- **Postsynaptic Signaling**
  (Stuart Cull-Candy / Yasunori Hayashi / Masanobu Kano)

TETRAPYRROLES, CHEMISTRY & BIOLOGY OF
SALVE REGINA UNIVERSITY
NEWPORT, RI
JUL 23-28, 2006
ANN SMITH, CHAIR
JUDITH BURSTYN, VICE CHAIR

- **Keynote Lecture**
  (James Kushner)
- **Biology of Linear Tetrapyrroles**
  (*Clark Lagarias* / André Verméglio / Stefan Hortensteiner)
- **Biochemical and Cellular Aspects of Tetrapyrrole Synthesis**
  (*Gloria Ferreira* / Martina Jahn / Andrew Dancis / Sam Beale / Martin Warren)
- **Novel Aspects of Tetrapyrrole Metabolism**
  (*Mark O'Brian* / Alison Smith / Alex Sheftel)
- **Tetrapyrroles in Complex Biological Processes**
  (*Harry A. Dailey* / Cheng Chi Lee / Peter J. Espenshade / Greg Anderson / Paula Fraenkel)
- **Tetrapyrrole Chemistry: Nanostructures and Artificial Heme-Proteins**
  (*David A. Lightner* / Dirk Guldi / Takashi Hayashi)
- **Tetrapyrroles as Regulators**
  (*Almira M. Correia* / Henry Krause / Kajuhiko Igarashi / Sadie Redding / Ruma Banerjee)
- **Tetrapyrrole Metabolism in Health & Disease**
  (*Janis Abkowitz* / Jawed Alam / Hani Atamna / Christoph Handshin)
- **Tetrapyrrole Trafficking**
  (*Judith Burstyn* / John Scheutz / Andrew T. McKie / Anne Lecroisey / Angela Wilks)

THEORETICAL BIOLOGY & BIOMATHEMATICS
TILTON SCHOOL
TILTON, NH
JUN 4-9, 2006
PAUL BRESSLOFF &
STEPHEN COOMBES, CO-CHAIRS
ERIC CYTRYNBAUM &
AARON FOGELSON, CO-VICE CHAIRS

- **Noise in Biological Systems**
  (*Andre Longtin* / Peter Swain / Paul Miller)
- **Biological Polymers and Membranes**
  (*Alex Levine* / Jefferey Fredberg / Fredrick Mackintosh / Robijn Bruinsma)
- **Biological Networks**
  (*Reka Albert* / Marc Vidal / Hamid Bolouri)
- **Social Insects**
  (*Fred Adler* / Martin Burd / Nigel Franks / Kern Reeve)
- **Ecological Stoichiometry**
  (*Roger Nisbet* / Christopher Kalusmeier / Edward McCauley / Tom Andersen)
- **Calcium Dynamics**
  (*James Sneyd* / Andrew Thomas / Martin Falcke / Gregory Smith)
- **Synaptic Plasticity**
  (*Jonathan Rubin* / Amitabha Bose / Rajesh Rao / Ila Fiete)
- **Cancer**
  (*Helen Byrne* / Alexander Anderson / Natalia Komarova / Kristin Swanson)
- **Special Session in Honor of Lee Segel**
  (*Rob de Boer* / Stephanie Forrest / Stan Maree / Rami Tzafriri)

THIN FILM & SMALL SCALE MECHANICAL BEHAVIOR
COLBY COLLEGE
WATERVILLE, ME
JUL 30-AUG 4, 2006
ZHIGANG SUO, CHAIR
RICHARD VINCI, VICE CHAIR

- **Mechanics of Integrated Structures**
  (*Oliver Kraft* / Ting Tsui / Jun He)
- **Small Scale Biomechanical Behavior I**
  (*Huajian Gao* / Rob Ritchie / Gang Bao)
- **Poster Preview I**
  (*Trevor Page*)
- **Plasticity and Stress in Confined Geometries I**
  (*Amit Misra* / Mike Uchic / Ke Lu)
- **Small Scale Biomechanical Behavior II**
  (*Jun Liu* / L. Mahadevan / Mary Boyce)
- **Poster Preview II**
  (*George Pharr*)
- **Plasticity and Stress in Confined Geometries II**
  (*Helena Van Swygenhoven* / Alan Needleman / Ed Webb)
- **Interaction Between Soft and Hard Materials I**
  (*Wole Soboyejo* / Sigurd Wagner / Yves Leterrier / Matt Begley)
- **Interaction Between Soft and Hard Materials II**
  (*Bob Keller* / Herbert Hui / Ray Pearson)
- **New Vistas of Small-Scale Mechanical Behavior**
  (*Erik van der Giessen* / Steve Granick / Manoj Chaudhury / John Bassani)
- **Liquid Crystal Elastomers**
  (*Reiner Dauskardt* / Mark Warner)

THIOL-BASED REDOX REGULATION & SIGNALING
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUN 18-23, 2006
VADIM GLADYSHEV, CHAIR
RUMA BANERJEE, VICE CHAIR

- **Thiol-Based Redox Systems**
  (Jon Beckwith / Arne Holmgren)
- **Thioredoxin and Glutathione Systems**
  (Bob Buchanan / Joseph Loscalzo)
- **Disulfide Bond Formation and Isomerization**
  (Jim Bardwell / Roberto Sitia / Hiram Gilbert)
- **Redox Regulation and Disease**
  (Nick Tonks / Jonathan Stamler / Leonard Herzenberg)
- **Redox Homeostasis**
  (Toren Finkel / Johannes Herrmann / Peter Cresswell)
- **Selenium and Sulfur in Redox Biology**
  (Dolph Hatfield / Elias Arner)
- **Mechanisms of Redox Signaling and Regulation**
  (Sue Goo Rhee / Michel Toledano / Brian Morgan)
- **Bioinformatics, Genomic and Proteomics in Redox Biology**
  (Todd Yeates / Pietro Ghezzi / Patsy Babbitt / Ursula Jakob)
- **Mechanisms of Thiol-Based Catalysis**
  (Katja Becker / Joris Messens / Leslie Poole)

TRIBOLOGY
COLBY COLLEGE
WATERVILLE, ME
JUN 18-23, 2006
TOM DICKINSON, CHAIR
KATHRYN WAHL, VICE CHAIR

- **Challenges to our Community**
  (*Trevor Page* / Andy Jackson / Peter Blau)
- **Biotribology**
  (*Nancy Burnham* / Jacob Klein / Dianne Rekow / Lisa Pruitt)
- **Contact Phenomena**
  (*Ali Erdemir* / Greg Sawyer / Ajay Kapoor)
- **Molecular Level Issues**
  (*Udo Schwarz* / Martin H. Müser / Mark Robbins / Steve Granick)
- **Tribochemistry**
  (*Larry Seitzman* / Steven Hsu / Eddy Tysoe)
- **Fundamental Studies of Friction**
  (*Roland Bennewitz* / Scott Perry / Ernst Meyer / Miquel Salmeron)
- **Nanodynamics and Nanotribology**
  (*Yip-Wah Chung* / Jackie Krim / Rob Carpick)
- **Adhesion, Rheology, and Sliding**
  (*Irwin Singer* / Andreas Polycarpou / Lionel Bureau / David Rigney)
- **Sonoluminescence and Mechanochemistry**
  (*Tom Dickinson* / Ken Suslick)

VIBRATIONAL SPECTROSCOPY
UNIVERSITY OF NEW ENGLAND
BIDDEFORD, ME
JUL 2-7, 2006
F. FLEMING CRIM, CHAIR
TIANQUAN LIAN &
PHILIP REID, CO-VICE CHAIRS

- **Vibrational Dynamics in Water**
  (Casey Hynes / Jim Skinner)
- **Vibrations Probing Bimolecules**
  (*John Straub* / Tom Rizzo / Marty Zanni / Sharon Hammes-Schiffer)
- **Vibrationally Driven Reactions**
  (*David Nesbitt* / Peter Hamm / Rainer Beck)
- **Vibrations of Hydrogen Bonded Systems**
  (*Michael Duncan* / Erik Nibbering / Mark Johnson / Heinrich Graener)
- **Vibrations at Interfaces**
  (Ken Eisenthal / Mary Shultz)
- **Intramolecluar Dynamics**
  (*Ned Sibert* / Brooks Pate / Martin Gruebele / Bob Field)
- **Vibrations of Molecules in the Environment**
  (*Phil Reid* / Veronica Vaida / Franz Geiger)
- **Vibrations of Confined Molecules**
  (*Ted Heilweil* / Nancy Levinger / Dana Dlott / Huib Bakker)
- **Retrospective and Prospective Views**
  (F.F. Crim / M. Quack / S.R. Leone)

WATER & AQUEOUS SOLUTIONS
HOLDERNESS SCHOOL
PLYMOUTH, NH
JUL 30-AUG 4, 2006
BRANKA M. LADANYI, CHAIR
ALAN K. SOPER, VICE CHAIR

- **Clusters and Nucleation**
  (Kenneth D. Jordan / Daniel M. Neumark / Barbara Wyslouzil)
- **Supercooled Water and Amorphous Ice**
  (Pablo Debenedetti / Hajime Tanaka / Christopher A. Tulk / John S. Loveday)
- **Solid Phases and Clathrates**
  (Victoria Buch / James P. Cowin)
- **Dynamics in Liquid Water**
  (Thomas Elsaesser / James T. Hynes / James L. Skinner / Keisuke Tominaga)
- **Hydrophobic and Surfactant Systems**
  (Max L. Berkowitz / Nancy E. Levinger / Alenka Luzar)
- **Liquid Interfaces**
  (Heather C. Allen / Brian Space / Richard J. Saykally / Douglas J. Tobias)
- **Aqueous Solutions and Mixtures**
  (Glenn J. Martyna / Imre Bako / Fabio Bruni)
- **Water Near Proteins and Membranes**
  (Robert G. Bryant / Benoit Roux / Dietmar Paschek)
- **Perspectives and Best Posters**
  (*Alan K. Soper*)

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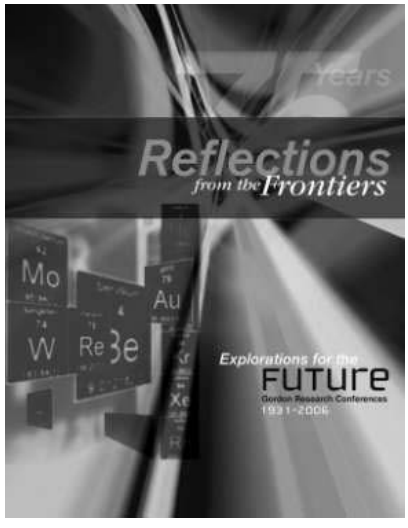
75 Years

at the

Frontiers of Science

Gordon Research Conferences is pleased to announce the release of a commemorative publication, *Reflections from the Frontiers*, chronicling our long and exciting history at the frontiers of science. Complementary copies will be provided to all GRC attendees in 2006 and 2007.

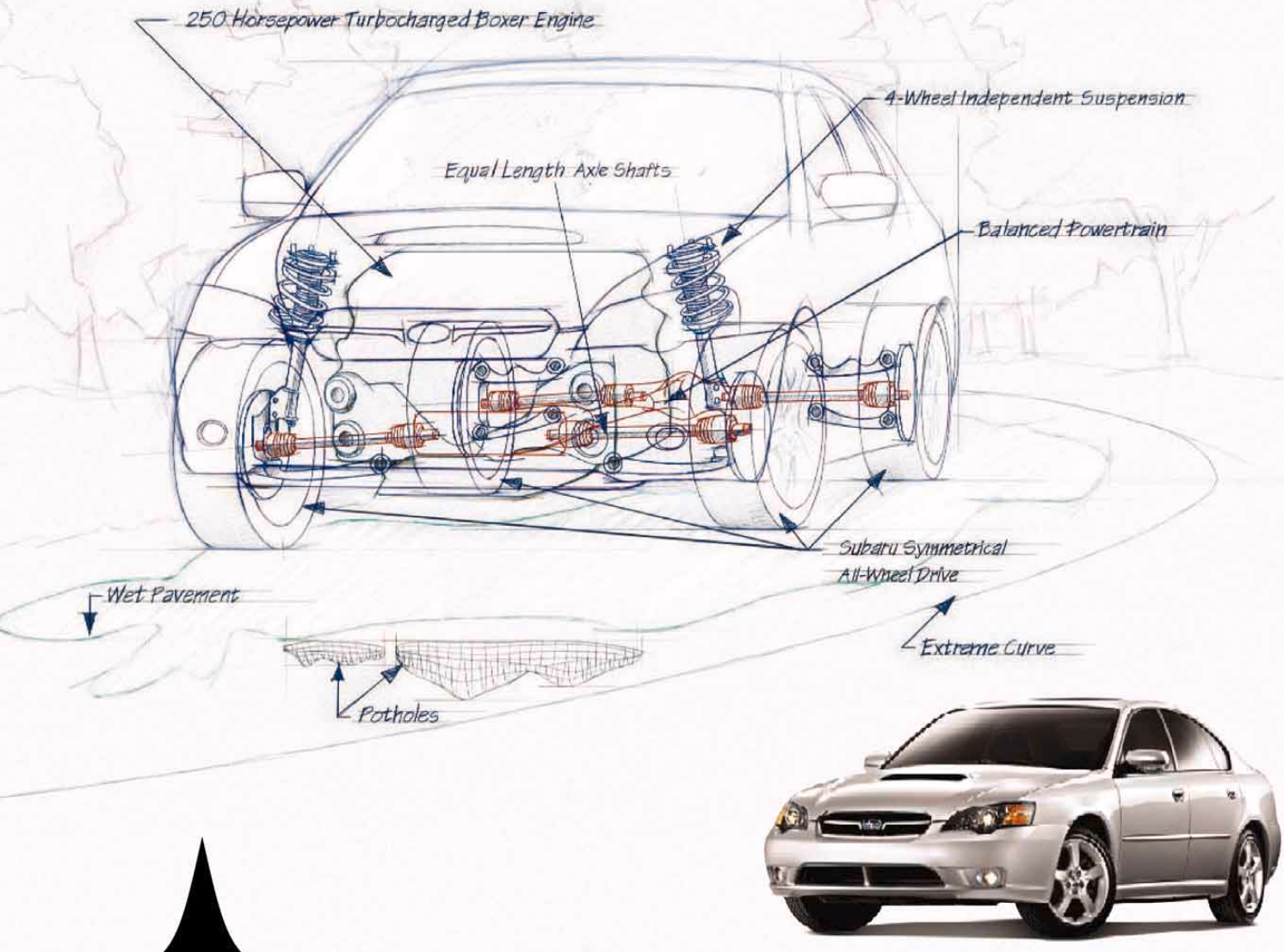


There has never been a better time to see what the excitement is all about. Be a part of history... come to a GRC!

2006 ALEXANDER M. CRUICKSHANK LECTURERS

Mark Ratner	Electron Donor Acceptor Interactions
Roger Tsien	Phosphorylation & G-Protein Mediated Signaling Networks
George Whitesides	Oscillations & Dynamic Instabilities In Chemical Systems
Linda Buck	Molecular & Cellular Neurobiology

Celebrating our 75th Anniversary on the Frontiers of Science (1931-2006)



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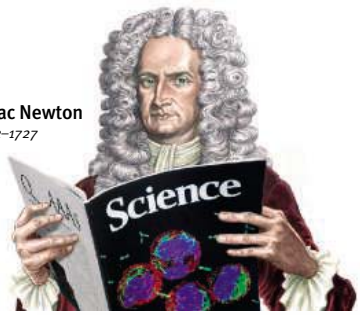

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POSITIONS OPEN

ASSOCIATE AND ASSISTANT PROFESSORS
Viral Oncogenesis

The Department of Microbiology and Immunology of the Chicago Medical School, Rosalind Franklin University of Medicine and Science, located in the northern suburbs of Chicago, invites applications for full-time, tenure-track appointments at the Associate and Assistant Professor levels in viral oncogenesis. We seek candidates to join a significant expansion of the Department in a newly built research building with state-of-the-art laboratories and facilities. Core resources include confocal, live-cell, and electron microscopy facilities, and a structural biology and proteomics center.

Candidates must have a Ph.D. or M.D. degree with training in viral oncogenesis and molecular virology. Candidates at the Associate Professor level must have a currently funded research program and a track record of federal funding. Candidates at the Assistant Professor level should show evidence of productive research accomplishments and demonstrated ability to pursue an independent research program. Successful candidates will receive competitive salaries and attractive startup packages, and are expected to develop and maintain an externally funded research program and teach at the medical and graduate level. Interested applicants should submit curriculum vitae, description of current and future research plans, copies of recent representative publications, and names and contact information of at least three references to: **Bala Chandran, Ph.D., Chair, Department of Microbiology and Immunology, The Chicago Medical School, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064.** Review of applications will begin immediately and will continue until the positions are filled. *Rosalind Franklin University of Medicine and Science is an Equal Opportunity/Affirmative Action Employer.*

POSTDOCTORAL POSITION
Beth Israel Deaconess Medical Center
Harvard Medical School

The Division of Viral Pathogenesis has a Postdoctoral position available February 1, 2006, to study immune mechanisms in AIDS vaccines and preclinical vaccine studies in nonhuman primates. The successful applicant will join a laboratory with an outstanding team of faculty that is solely focused on AIDS virus pathogenesis and vaccine development. The applicant should have Ph.D. or M.D., be motivated, organized, and able to work independently. Knowledge of BL-2 work procedures, basic molecular biology, and flow cytometry are required. Please send a letter of application, current curriculum vitae, along with names of three references and a one-page statement of career aspirations to: **Dr. Joern E. Schmitz, Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center, RE-213D, 41 Avenue Louis Pasteur, Boston, MA 02115,** or **e-mail: jschmitz@bidmc.harvard.edu.**

The Beth Israel Deaconess Medical Center is an Equal Opportunity Employer.

ASSISTANT PROFESSOR

Stony Brook University's Marine Sciences Research Center invites applications for a tenure-track Assistant Professor position in marine animal diseases. Required: Ph.D. or equivalent, and experience in research and diagnosis of aquatic diseases, preferably involving the use of molecular tools in finfish or crustaceans. Send statement of interest, curriculum vitae, and three letters of reference to: **Bassem Allam, Chair of the Marine Pathologist Search, Marine Sciences Research Center, Stony Brook University, Stony Brook, NY 11794-5000.** Application review begins March 15, 2006. Visit **website: http://www.stonybrook.edu/cjo** for full employment information. *Affirmative Action/Equal Opportunity Employer.*

POSITIONS OPEN

ASSISTANT/ASSOCIATE PROFESSORS
for Biology and Chemistry

The College of Sciences at the University of Findlay is seeking candidates for two tenure-track appointments at the Assistant or Associate Professor level: one in biology and one in chemistry. Applicant review will begin immediately and the positions will start in August 2006.

The biology candidate must have a Ph.D. in the biological sciences with strengths in physiology and microbiology. Teaching responsibilities could include classes in the areas of general biology, anatomy and physiology, zoology, genetics, microbiology, and research methods. Research opportunities are available at both the undergraduate and graduate level. The biology area provides instruction to students majoring in biology, pre-veterinary studies, pharmacy, forensic science, environmental science, and other health professions areas.

The chemistry candidate must have a Ph.D. in chemistry with specialization in physical, analytical, or inorganic chemistry. Responsibilities would include course and laboratory curriculum development, leadership in undergraduate student research, and teaching in our newly approved undergraduate chemistry major. Teaching assignments will be in the areas of physical and general chemistry with other areas based on the candidate's background. Current laboratory facilities include general chemistry labs and a newly renovated organic chemistry lab. Plans are being developed for the addition of a physical/inorganic chemistry laboratory and the renovation of an existing analytical laboratory as the program seeks Amercian Chemical Society (ACS) certification. The chemistry area currently serves majors in the area of pre-veterinary studies, pharmacy and forensics, as well as chemistry and other applied science majors.

College teaching experience is desirable and a commitment to excellence in teaching and scholarly activity is expected. Rank and salary will be commensurate with qualifications. The University of Findlay is a comprehensive Master's degree institution which has grown from 1,500 to more than 4,500 students in the last twenty years, and is now the largest private university in northwest Ohio. Nearly one-third of the University's students major in the applied and basic sciences or pharmacy and other health professions. Applicants should submit a letter of application, curriculum vitae, statement of teaching philosophy, and the names of three references to: **Mary Jo Geise, Dean of the College of Sciences, The University of Findlay, 1000 North Main Street, Findlay, Ohio 45840,** or via **e-mail: geise@findlay.edu.** *The University of Findlay is an Equal Opportunity Employer and Educator.*

POSTDOCTORAL RESEARCH ASSOCIATE POSITION

Postdoctoral Research Associate position is available immediately to study the molecular basis of BHV-1 neuropathogenesis and to construct recombinant BHV-1 expressing bacterial and other viral antigens for vaccine use. The position is renewable for two to three years. Ph.D. or equivalent and *valid work visa* desired. Experience in construction of recombinant viruses using infectious BAC clones is desirable. Screening of applicants begins February 1, 2006. Send curriculum vitae and e-mail addresses of three references to: **Shafiqul Chowdhury, D.V.M., Ph.D., Pathobiology, K-231 Mosier Hall, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506. Telephone: 785-532-4616; fax: 785-532-4039; e-mail: chowdh@vet.k-state.edu.** *Paid for by Kansas State University.*

The Department of Biological Sciences at **Salisbury University** is accepting applications for a **TENURE-TRACK POSITION** in human anatomy and physiology at the rank of **ASSISTANT PROFESSOR,** starting fall 2006. A Ph.D. and evidence of the potential for excellence in teaching and research will be required. For further information, please see the Salisbury University **website: http://www.salisbury.edu/hr/Jobs/default.asp?asearch=faculty.**

Positions @ NIH
THE NATIONAL INSTITUTES OF HEALTH

Branch Chief Positions
National Human Genome Research Institute

The National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) is seeking one or two dynamic and experienced senior investigators to serve as Branch Chiefs in its Intramural Program. The Division of Intramural Research at NHGRI is a world-class, highly collegial research environment, where basic and clinical research is performed in a highly integrative fashion in the broad areas of genetics, genomics, diagnostics, and therapeutics.

The successful candidate(s) will have significant leadership responsibilities, involving the oversight of an existing cadre of investigators with research programs in human genetics, developmental genetics, chromosome biology, gene therapy, immunology, neuroscience, and stem cell biology as well as leading future recruitment efforts. A vision for crafting cutting-edge research programs that advance the frontiers of genetics and genomics will be key. In addition to superlative scholarship, the successful candidates must have well-honed administrative skills to lead a large and diverse research program.

These fully funded, tenured positions will include appropriate start-up allowances, an ongoing commitment of clinical and laboratory resources, and positions for support staff and trainees. In addition to the resources of the NIH Clinical Research Center, there will be full access to NHGRI core facilities. Candidates must have an M.D., Ph.D., or equivalent degree, as well as advanced training and demonstrated accomplishment in genetic and/or genomic research.

Interested applicants should submit their curriculum vitae, a three-page description of their research program, and three letters of recommendation through our online application system, at http://research.nhgri.nih.gov/apply.

The closing date for these positions is March 1, 2006.

For more information about the NHGRI Intramural Program, please see http://www.genome.gov/DIR
Specific questions regarding these positions may be directed to Dr. Andy Baxevanis (Search Chair) at andy@nhgri.nih.gov or by fax (301-480-2634).

Tenured Position in Clinical Neurobiology
National Institute of Environmental Health Sciences
Research Triangle Park, North Carolina

The Laboratory of Neurobiology in the Division of Intramural Research at NIEHS is recruiting a Tenured Clinical Investigator to establish a high-quality, independent research program on clinical aspects of neurological sciences and disease. Ideally, studies would be conducted on the identification and prevention of environmental disruption of human cognitive potential at any life stage, including early development, childhood learning, or neurodegenerative processes associated with aging. To be considered applicants must have an M.D. or a Ph.D. degree or both, a clinically focused research proposal, postdoctoral experience in clinical research, and a strong publication record. Applicants combining clinical or epidemiological studies with more basic laboratory studies of molecular and cellular aspects of neurobiology, including work with model organisms, are particularly encouraged to apply. The NIEHS has state-of-the-art core facilities for research and an outstanding cadre of epidemiologists and biostatisticians. Excellent start-up funds, salary, and benefits package will be provided. Interested persons should send their curriculum vita with a statement of research accomplishments and plans, and arrange for letters of recommendation (at least 6 from non-collaborators) to be submitted to the address below. The letters should be from leaders in the field who specifically address recommendation for a tenured position at NIH. For information concerning the Laboratory of Neurobiology, access website http://dir.niehs.nih.gov/dirln/.

Applications received by **March 3, 2006** will be given first consideration. Applications received after that date will be considered only if the position has not been filled.

Applications and letters should be sent to: **Ms. Cindy Garrard (DIR 06-01), National Institute of Environmental Health Sciences, P.O. Box 12233, Maildrop A2-06, 111 Alexander Drive, Room A206, Research Triangle Park, NC 27709. E-mail: dir-appls@niehs.nih.gov**

Clinical Director
Intramural Research Program
National Institute of Mental Health

The National Institute of Mental Health (NIMH) seeks a highly accomplished senior clinician to be Clinical Director. The position comes with complementary budget and staff. The strong scientific environment and outstanding resources at NIMH for carrying out such a program make this a unique opportunity for a senior clinician. The position also offers unparalleled opportunities for interdisciplinary collaboration with scientists throughout the NIH. The successful candidate will be expected to strengthen the current program.

Applicants should have: a M.D. degree; broad clinical experience, including a record of high clinical achievements, national and international recognition for those achievements, and experience in direct administration of a clinical program.

Salary is commensurate with experience and accomplishments, and a full Civil Service package of benefits (including retirement, health, life, and long-term care insurance, as well as a Thrift Savings Plan, etc.) is available. NIMH is a major research component of the National Institutes of Health and the Department of Health and Human Services, which have nationwide responsibility for improving the health and well being of all Americans. Interested applicants should send curriculum vitae, bibliography, statement of research interests, accomplishments, and goals, together with six letters of reference to: **Dr. Robert Innis, Chair, Search Committee for Clinical Director, Bldg. 1, Rm. B3-10, NIH, Bethesda, MD 20892-1366; or email to innisr@mail.nih.gov**
Application deadline: **March 3, 2006.**

WWW.NIH.GOV

Director, Office of Intramural Training and Education, NIH

The Intramural Research Program of the National Institutes of Health (NIH) is seeking an outstanding individual to serve as Director of the Office of Intramural Training and Education (OITE). The OITE oversees the education of trainees at all levels in the NIH Intramural Research Program, from high school students to postdoctoral fellows, and coordinates and supplements the efforts of the Intramural Research Programs of the individual Institutes and Centers to enhance the training experience at NIH and the visibility of NIH for the next generation of scientists and physicians. Working with the NIH Institutes and Centers, the Director will identify new developments and national trends in training and help to integrate these into the agency's biomedical research mission. The Director will oversee the establishment and implementation of creative strategies for recruiting clinician and scientist trainees, particularly those from populations currently under-represented in biomedicine.

The Director chairs the Intramural Training Committee and oversees an office of ~30 staff, with three major areas of responsibility: the Graduate Partnerships Program, the Medical Education Program, and the Fellowship Training Program. Further details about OITE and specific programs can be found at www.training.nih.gov.

The Director of OITE must have a doctoral-level degree, significant research productivity, and mentoring and training experience. Administrative experience in overseeing biomedical research training and mentoring is desirable. The possibility of research resources and appointment is subject to negotiation. Salary will be commensurate with experience.

Please send applications (statement of interest, CV, bibliography, and names of three references) to **Dr. Joan P. Schwartz, Office of Intramural Research, NIH, Building 1- Room 152, Bethesda, MD 20892-0151 (phone 301-496-1248). Applications are due by March 31, 2006.**

Address questions to **Dr. Michael Gottesman, Deputy Director for Intramural Research, Office of the Director, NIH (phone 301-496-1921).**

Division of Cancer Biology
Cancer Etiology Branch
Chemist/Microbiologist/Biologist

With nation-wide responsibility for improving the health and well being of all Americans, the Department of Health and Human Services (DHHS) oversees the biomedical research programs of the National Institutes of Health and those of NIH's research Institutes.

The National Cancer Institute (NCI) at the NIH is seeking a Chemist, Microbiologist, or Biologist to fill the position of Chief in the Cancer Etiology Branch (CEB). This branch administers a large portfolio of research grants covering a broad spectrum of topics directed at understanding the biological basis of cancer, emphasizing cancer etiology, biological and chemical carcinogenesis. The Branch Chief uses expert knowledge of the research field and administrative experience to provide the Branch with leadership, direction, coordination and perspective as well as to respond to NCI leadership. The Chief develops initiatives in the area of scientific responsibility, establishes program priorities, evaluates program effectiveness, provides information, advice and consultation to individual scientists and institutional management officials relative to NIH and NCI funding, provides NCI leadership with recommendations concerning funding needs, priorities and strategies, and organizes meetings and workshops to further program objectives.

A full Civil Service package of benefits (including health and life insurance options, retirement, paid holidays, vacation and sick leave) is available.

The NCI vacancy announcement for this position contains complete application procedures and lists all mandatory information, which you must submit with your application. To obtain the vacancy announcement for this position which will be available on **01/06/2006** and posted under announcement **#NCI-05-104816**, you may visit the website **https://www.usajobs.opm.gov**. Questions can be directed to **Eugene McDougal on (301) 435-5722**. Please see vacancy announcement for application submission requirements.

Staff Scientist Position
National Heart, Lung, and Blood Institute (NHLBI)

The National Heart, Lung, and Blood Institute, a major component of the NIH and the DHHS, is recruiting for a Staff Scientist within the Pulmonary-Critical Care Medicine Branch to join a group of investigators examining the molecular and cellular biology of vesicular trafficking, guanine nucleotide-binding proteins, and post-translational modification of proteins. The successful candidate should have a Ph.D. or M.D. with experience in molecular and cellular biology, prior studies involving protein isolation and characterization, and expertise with transgenic animals.

The focus of the research is on the functions of guanine nucleotide-binding proteins and post-translational modification of proteins in the vesicular trafficking process. Specific areas of focus include the extended ADP-ribosylation factor (Arf) family of guanine nucleotide-binding proteins, the guanine nucleotide-exchange proteins (GEPs) for Arfs, and mechanisms of post-translational modification in regulating protein targeting and turnover.

Salary is commensurate with research experience and accomplishments. A full package of benefits (including retirement, health, life, and long-term care insurance, Thrift Savings Plan participation, etc.) is available. Applicants should send a CV, a brief statement of research interests, and the names of three references to: **Vincent Manganiello, Chair, Search Committee, NHLBI-NIH, Building 10, Room 5N307, MSC 1434, NHLBI, National Institutes of Health, Bethesda, MD 20892, manganiv@nhlbi.nih.gov**

GEORG-AUGUST-UNIVERSITÄT GÖTTINGEN
Bereich Humanmedizin

Universitätsklinikum – Medizinische Fakultät

UKG

In the Department of Molecular Oncology of the Medical Faculty within the Göttingen Center for Molecular Biosciences (GZMB) of the Georg-August-University Göttingen, a position of a

JUNIOR PROFESSOR FOR MOLECULAR CANCER RESEARCH AND CELL REGULATION
(SALARY GROUP W1)

is to be filled as soon as possible.

The successful candidate can already present outstanding scientific successes and will now establish an independent research program. Research areas should in some way address the molecular mechanisms of tumor development, but broadly related topics will be considered depending on a candidate's excellence. We offer adequate in-house support (including a technician's position) and access to state-of the art facilities, e. g. life cell microscopy, animal housing, arrays, etc. Further information about the department can be found at http://www.gzmb.uni-goettingen.de/faculty/f_dobbelstein.html.

Proficiency in German would be helpful but is not a prerequisite, since most teaching activities will address international curricula with English as a teaching language.

Legal aspects of the hiring process are covered by NHG, Nds. GVBl. 19/2002, S. 286 ff. and will be explained upon request. The University of Göttingen is an equal opportunity employer. Female applicants are encouraged to apply and will be given preference in case of equal qualification, within the legal possibilities. Disabled applicants will be given preference in case of equal qualification. Part time employment might be possible.

Applications including CV, publication list, current funding (if any), references and a short description of planned research work should be submitted within four weeks after the publication of this advertisement to the **Dean of the Medical Faculty, Georg-August-Universität, Robert-Koch-Str. 42, 37075 Göttingen, Germany.**

Please fill in as well the following form:
http://www.humanmedizin-goettingen.de/orga/doc/curriculum_vitae-kurzbewerbungsbogen.doc

United Nations Educational, Scientific and Cultural Organization

HEAD OF THE COORDINATION UNIT FOR TSUNAMI OF THE INTERGOVERNMENTAL OCEANOGRAPHIC COMMISSION (IOC) of UNESCO

The Intergovernmental Oceanographic Commission (IOC) of UNESCO is recruiting the Head of the Coordination Unit for Tsunami to be based in Paris, France. Under the authority and the general supervision of the Assistant Director General of UNESCO and Executive Secretary of the IOC, based on the relevant decisions of the IOC General Assembly and in co-operation with the IOC programmes and sections concerned, the incumbent will organize, plan and secure resources to implement the IOC Tsunami Programme.

Qualifications and experience required:

- Advanced university degree, preferably at PhD level or equivalent in Physical Oceanography, Engineering or Earth Sciences.
- Proven management experience heading a major national programme, centre or agency dealing with marine hazards. Research or operational experience in tsunami hazards is highly desirable.
- At least ten years of professional experience in the management and coordination of operational oceanic and/or geophysical systems including observation, detection, and data management components; proven ability to link these systems to stakeholders' needs either in the public or private sector.
- Experience at working in an international or intergovernmental environment.
- Ability to effectively lead a team in a focused manner to provide support services to the multi-cultural Intergovernmental Coordination Groups for Tsunami Warning Systems (ICG's/TWS) around the globe.
- Ability to responsibly plan, organize and manage a unit with minimum direct supervision. Good IT skills as well as worldwide travel mobility are required.
- Excellent knowledge of English or French is required.

Salary and allowances:
Contract will be as an Appointment of Limited Duration (ALD) at P5 level, for two (2) years, renewable up to a maximum of four (4) years. Subject to staff member status, the ALD provides adequate social security coverage and medical care.
E-mail applications to be sent to p.bernal@unesco.org with "Head of Tsunami Unit" on the subject. Enquiries by phone to +33-1-45.68.39.83

Written applications, in English, which should also include date of birth, gender, nationality, should be addressed to: **Patricio Bernal, Executive Secretary, Intergovernmental Oceanographic Commission/UNESCO, 1 Rue Miollis, 75732 Paris CEDEX 15, no later than 28 February 2006**. Only candidates being seriously considered will receive an acknowledgement. Please mark envelope "Head of Tsunami Unit Post".

HEAD OF THE UNESCO/IOC SECRETARIAT TO THE INTERGOVERNMENTAL COORDINATION GROUP FOR THE INDIAN OCEAN TSUNAMI WARNING AND MITIGATION SYSTEM (ICG/IOTWS)

The Intergovernmental Oceanographic Commission (IOC) of UNESCO is recruiting the Head of the UNESCO/IOC Secretariat to the Intergovernmental Coordination Group for the Indian Ocean Tsunami Warning and Mitigation System (ICG/IOTWS) to be based in Perth, Australia. Under the oversight of Assistant Director General of UNESCO and Executive Secretary of the IOC, and under the supervision of the Head of the Coordination Unit For Tsunami, based on the relevant decisions of the IOC General Assembly and in co-operation with the IOC programmes and sections concerned, the incumbent will organize, plan and secure resources to implement the IOC Tsunami Programme in the Indian Ocean.

Qualifications and experience required:

- Advanced university degree, in Ocean or Geophysical Sciences.
- At least ten years of professional experience in the operation and/or management of ocean and/or geophysical systems such as observation, detection, and communication networks.
- Proven ability to manage resources, prepare reports, and make effective presentations.
- Demonstrated high quality interpersonal skills.
- Experience at working in an international environment or intergovernmental relations will be an advantage.
- Ability to effectively lead a small team in a focused manner to provide support services to the multi-cultural ICG/IOTWS.
- High-level command of English is essential.

Salary and allowances:
Contract will be as an Appointment of Limited Duration (ALD) at P4 level, for two (2) years, renewable up to a maximum of four (4) years. Subject to staff member status, the ALD provides adequate social security coverage and medical care.
E-mail applications to be sent to p.bernal@unesco.org with "ICG/IOTWS Technical Secretary Post" on the subject. Enquiries by phone to +33-1-45.68.39.83

Written applications, in English, which should also include date of birth, gender, nationality, should be addressed to: **Patricio Bernal, Executive Secretary, Intergovernmental Oceanographic Commission/UNESCO, 1 Rue Miollis, 75732 Paris CEDEX 15, no later than 28 February 2006**. Only candidates being seriously considered will receive an acknowledgement. Please mark envelope "ICG/IOTWS Technical Secretary Post".

UCLA The University of California, Los Angeles, School of Dentistry invites applications for the full-time tenured position of Chair of the Division of Oral Biology and Medicine. The division is research intensive and committed to broadening the scientific education of the UCLA dental student and providing fundamental research training for graduate dentists and oral health researchers pursuing the MS or PhD degree in oral biology. Candidates must have a strong scientific background with a substantial research record and active funding. Ability and track record to collaborate in interdisciplinary and multidisciplinary research is highly desirable. Areas of basic research emphasis within the division include head and neck cancer, bone biology and bioengineering, and microbiology and immunology. Applicants must have at least one of the following degrees: DDS/DMD or foreign equivalent dental degree; MD; or PhD. A record of previous administrative experience is desirable. The rank and salary will be commensurate with the candidate's qualifications and experience. Opportunity with intramural practice is available for an individual with a California dental license or a board-eligible or board-certified specialist.

Applicants should submit a curriculum vitae and the names of three references to: **Dr. John A. Yagiela, Professor and Chair, Division of Diagnostic and Surgical Sciences, UCLA School of Dentistry, Box 951668, Los Angeles, CA 90095-1668**.

The University of California is an Equal Opportunity and Affirmative Action Employer. All qualified applicants are encouraged to apply.

RESEARCH SCIENTIST BIOANALYTICAL TEST DEVELOPMENT

Incumbent will lead and manage a development program for establishing "Well Characterized Master References" for *in vitro* potency testing of inactivated viral and bacterial vaccines. Individual will propose and implement strategies for development of biochemical and immunological assays used to quantitatively and qualitatively characterize the reference preparations that are employed to release vaccine products by *in vitro* assays. A major part of the program will be validation studies on the assays to determine their level of accuracy and precision prior to transfer to Quality Control, and regulatory approval. The selected candidate will lead a team of two technical personnel and will manage all reporting phases of the project. Strong communication skills will be required. The ideal candidate will have a Ph.D and training in biochemistry, immunology, or microbiology with experience in analysis of proteins and biomolecules, or M.S. degree in biochemistry, immunology, or microbiology, and 5 – 6 years experience in the biotechnology industry in analysis of proteins.

To apply online, please visit our website at **www.merial.com**. Indicate reference number **#1391BR** on your application. Additional positions are advertised on our website. Alternatively, mail an application to: **Merial Limited, 1730 Olympic Drive, Athens, GA 30601, or Fax to (706) 227-4187**. Merial is a joint venture between Merck & Co., Inc. and sanofi-aventis.

DIRECTOR

University of Michigan Ann Arbor

Graham Environmental Sustainability Institute

The University of Michigan (UM) seeks a full-time Director for its newly created Graham Environmental Sustainability Institute. The Graham Institute is a University-wide unit with the mission of promoting interdisciplinary research and education in environmental sustainability related fields, providing financial support to encourage outstanding students to incorporate environmental sustainability issues into their studies, and developing outreach programs that demonstrate the University's environmental sustainability commitment. UM is exceptionally well positioned to lead both research and educational efforts in environmental sustainability. Presently, over 300 faculty members in seven schools focus on environmental sustainability related research and education, including studies in the biological, physical, and social sciences; engineering and design, business, public health, and policy.

UM is seeking an outstanding individual at the full professor level to provide leadership in environmental sustainability that will: (1) increase interdisciplinary research and educational opportunities; (2) attract the best students and researchers to the University of Michigan; (3) support and encourage new courses and degree programs at both the undergraduate and graduate level; and (4) develop new strategic initiatives.

The Graham Institute Director will have a faculty appointment(s) in his/her field(s) of scholarly expertise, and as the Institute Director, report to the Office of the Provost. The qualifications of the successful candidate should include a combination of:

- National/international recognition as a researcher and educator in a discipline(s) related to environmental and environmental sustainability studies.
- A demonstrated ability to promote research and educational collaboration across diverse disciplines.
- Administrative experience, including the ability to develop new funding opportunities.
- A demonstrated ability to forge effective relationships among the Institute's constituencies, including academia, industry, non-governmental organizations, and governmental agencies.

Nominations and applications will be confidentially reviewed beginning February 1, 2006, and will be accepted until the position is filled. Individuals from underrepresented groups are encouraged to apply. Application materials should include a letter addressing how the candidate's experience matches the position requirements, a curriculum vitae, and a vision statement. Materials and inquiries should be submitted, preferably electronically, to:

Deborah Goldberg
Professor and Chair, Ecology and Evolutionary Biology
Chair, Graham Institute Director Search Advisory Committee
University of Michigan
5086 Fleming Administration Building
Ann Arbor, MI 48109-1340
gesi.search.chair@umich.edu

The University of Michigan is an equal opportunity/affirmative action employer.

Research Faculty Positions

CARCINOGENESIS and CUTANEOUS ONCOLOGY & IMMUNOLOGY

The Cardinal Bernardin Cancer Center of Loyola University Medical Center, is seeking outstanding candidates to fill tenure track faculty positions at the Assistant or Associate Professor level within two of our Oncology Institute's four basic science research programs.

Candidates for our **Carcinogenesis Program** should have expertise in the areas of molecular epidemiology, genetic linkage analyses, molecular biology/immunology, and/or mineral fiber carcinogenesis. This laboratory based program, under the direction of Dr. Michele Carbone, is complemented by an established clinical program in the area of Thoracic Oncology. The Carcinogenesis Program studies how environmental carcinogens, biological carcinogens, and genetics interact in the pathogenesis of cancer.

Our **Cutaneous Oncology & Immunology Program** is seeking candidates to augment its investigation of melanoma and squamous cell carcinoma. The laboratory based program, under the direction of Dr. Brian Nickoloff, is complemented by an established clinical program in the area of Skin Cancer.

Successful candidates must have developed an innovative research program and publication track record, and will be expected to develop and maintain independently NIH/NCI funded laboratory research operations, as part of these programs. In addition to a generous start up package and laboratory space, the Cardinal Bernardin Cancer Center provides a collegial, highly interactive, and friendly research environment, with opportunities for translational research with a strong clinical enterprise. Nationally funded investigators will be given preference.

The Medical Center campus, located just west of Chicago, is comprised of Loyola University's Stritch School of Medicine and related inpatient and outpatient facilities. The 125,000 sq. ft. Cancer Center houses both research laboratories and outpatient clinics. Additional information about the Oncology Institute can be found online at www.luhs.org/oncinstitute .

Interested applicants may send CV, publications list, funding history, statement of research interests, and the names of three references to:

Michele Carbone, M.D., Ph.D.
Director, Carcinogenesis Program
or
Brian J. Nickoloff, M.D., Ph.D.
Director, Cutaneous Oncology & Immunology Program

LOYOLA UNIVERSITY CHICAGO

c/o Maggie Storti,
Administrative Assistant
Cardinal Bernardin Cancer Center
Loyola University Medical Center
2160 S. First Avenue
Maywood, IL 60153

An Equal Opportunity Employer/Educator

University of Massachusetts Medical School
UMASS

TENURE-TRACK NEUROSCIENCE POSITION

The Brudnick Neuropsychiatric Research Institute (BNRI), established as part of the unprecedented research expansion at the University of Massachusetts Medical School, invites applications for a tenure-track position at the level of Assistant/Associate Professor. The BNRI was established in 2000 as a division of the Department of Psychiatry and is committed to broad based research investigating basic neurobiological principles underlying psychiatric disorders. Faculty interests focus on a variety of neurobiological problems and psychiatric disorders, with a common theme in the neurobiology of addiction. Applicants whose interests focus on addiction are especially welcomed, particularly those with a strong behavioral component. The BNRI is integrated into the Interdepartmental Neuroscience Program, which provides opportunities for graduate training and interactions with a large group of multidisciplinary neuroscientists. The BNRI is housed in a state-of-the-art laboratory facility, which includes magnets for high resolution functional brain imaging. The successful candidate is expected to establish an independent research program and play an integral role in new program initiatives. The position is highly competitive with regard to salary, start-up funds, and laboratory space.

Applicants should send a CV, statement of research interests, and names and addresses of three references to:

Dr. Steven Treistman, Director
Brudnick Neuropsychiatric Research Institute
University of Massachusetts Medical School
303 Belmont Street
Worcester, MA 01604

E-mail: bnri@umassmed.edu
www.umassmed.edu/bnri

An Equal Opportunity/Affirmative Action Employer.

U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment (NCEA)

Supv. Biologist/Toxicologist/Health Scientist/Physical Scientist/Mathematical Statistician

Ez hire Announcement #RTP-DE-2006-0048 or RTP-MP-2006-0080

The U.S. Environmental Protection Agency is seeking highly qualified applicants for two Branch Chief positions with the National Center for Environmental Assessment (**http://cfpub.epa.gov/ncea/**) which are located in Cincinnati, Ohio. Duties include supervision and leadership of an interdisciplinary team of scientists conducting high-profile human health and ecological assessments and developing cutting-edge risk assessment methods, with emphasis on water quality and hazardous waste.

Excellent benefits: The selected candidate will be eligible for a full benefits package, including paid relocation, health insurance, life insurance, retirement, and vacation and sick leave. This is a permanent, full time position. U.S. citizenship is required.

Salary Range: The salary range is $91,080 to $139,275 (GS 14/15) per year, commensurate with qualifications.

Qualifications: A bachelor's degree (or higher) is required. Desirable applicants will have an advanced degree and demonstrated experience in conducting research and leading research teams in environmental health, toxicology, biology, physical science, mathematical statistics, or a related field.

How to Apply: Applicants should apply through Ezhire at **http://www.epa.gov/ezhire** Select apply for jobs. If you are already registered in Ezhire@EPA system, access the vacancy announcement through Registered Users. Otherwise, select New Users and complete the registration process. The vacancy announcement will be open through March 13, 2006. Application materials must be submitted with 48 hours from the closing date of the announcement. You need to submit the additional documentation described in the full text vacancy. Questions regarding this vacancy may be directed to **Joann Kelleher, Human Resources Management Division** at **kelleher.joann@epa.gov**.

The US EPA is an Equal Opportunity Employer.

EUROPEAN SCIENCE FOUNDATION

Position Announcement

Head of Unit/Scientific Secretary of the Standing Committee for Life, Earth and Environmental Sciences (LESC)

ESF is inviting applications for the position of Head of the LESC Unit. The LESC Unit is one of five science Units in ESF. The European Science Foundation, established in 1974, is an association of 78 research funding and performing organisations and academies in 30 European countries, located in Strasbourg, France. Its mission is to advance European research and to explore new directions for research at the European level. It provides a platform for its Member Organisations and promotes science of the highest quality through strategic foresight, science policy development, networking of scientists and managing research programmes in all fields of science.

Profile and recruitment

The successful candidate should have:

- Proven experience at senior level in the field of the Earth and Life Sciences (encompassing Molecular and Cell Biology, Functional Genomics, Systems Biology, Ecology, Earth Sciences, Climate Research and Environmental Research): in scientific research (with preference an in-depth knowledge in the molecular life sciences gained through personal research at post doctoral level, plus a broad overview of science in the LESC field), in science policy, and in the management of grants schemes
- Good knowledge of European and international research structures and institutions, in particular in the field of LESC, as well as of national funding organisations
- Proven management experience with strong interpersonal and communications skills, a team work attitude and the ability to work in a multicultural environment
- Excellent spoken and written English. Working knowledge of French and other European languages would be an advantage but is not a requirement

Tasks and responsibilities

The Head of Unit reports to the Director of Science and Strategy. The principal tasks include:

- Acting as the Secretary to the Standing Committee for Life, Earth and Environmental Sciences of the ESF
- Developing proposals for new LESC activities, including new science policies, strategic frameworks for the LESC domain, scientific activities and interdisciplinary initiatives with other science domains
- Implementing the policies of LESC within the ESF context
- Work closely with the CEO Unit, which includes membership of the ESF Management Group
- Responsibility for peer review processes at a high quality level
- Managing the staff and the budget of the LESC Unit
- Liaison with ESF Member Organisations, ESF Committees, COST Technical Committees and external bodies relevant to the LESC domain like the Commission and EMBO

Employment conditions

- The full-time position is offered for a three-year term, with the possibility of a prolongation of two years, preferably starting 1 June 2006
- The place of work is Strasbourg and the job will involve a significant amount of travel
- The salary level will be based on experience and qualifications of the successful candidate and will follow ESF terms and conditions

Contact person: Dr. John Marks

For further information about ESF see www.esf.org

Applications by **28 February 2006** to: ESF, Human Resources Unit,1 quai Lezay-Marrnésia, BP 90015, F-67080 Strasbourg cedex or *jobs@esf.org*

Faculty Position in Proteomics

Stony Brook University's Department of Pharmacology is seeking faculty candidates with outstanding research experience in the area of proteomics.Candidates are encouraged to apply for a position at the level of Assistant or Associate Professor. As a tenured or tenure-track investigator, this individual will be expected to have, or to develop, a successful independent research program using state-of-the-art proteomic methods and to contribute to the teaching responsibilities of the Department. Candidates are encouraged to review the broad research interests of current faculty members (see *www.pharm.sunysb.edu/faculty*) to evaluate the prospects for future collaborative research. The successful candidate will work closely with the University Proteomics facility which is equipped with Voyager DE-Str MALDI-TOF, Applied Biosystems Q-Star LC-MS/MS, and SELDI instruments. The position offers a generous startup-package and long-term salary support. It is anticipated that additional instrumentation will be acquired to support this recruitment. **Required:** M.D. or Ph.D. degree (or equivalent) with at least two years of postdoctoral research experience at the Assistant Professor rank; experience commensurate with a tenured position is required at the Associate Professor rank. Hands-on experience in sample preparation, mass spectrometric protein sequencing, and data analysis must be documented by appropriate publications in leading journals. A research focus relevant to the Long Island Cancer Center or to developing programs in diabetes and endocrine research is preferred.

Review of applications will commence on April 7, 2006, and will continue until the vacancy is filled.

To apply, applications should be submitted electronically to: *proteomics_search@pharm.stonybrook.edu.*

The application should consist of a single PDF file containing: (1) a CV; (2) a three-page synopsis of major research accomplishments and future research plan; (3) name, address, and e-mail addresses for three individuals who have agreed to write letters of recommendation; and (4) a cover letter indicating whether the applicant wishes to be considered for appointment at the Assistant or Associate Professor level (applicants at the Associate Professor level should include a summary of past and current research funding).

AA/EOE. Visit *www.stonybrook.edu/cjo* for complete job description and other employment opportunities.

STONY BROOK

Ontario Institute for Cancer Research

PRESIDENT and SCIENTIFIC DIRECTOR

A rare and exciting opportunity to build a new cancer research institute to eventually include 50+ investigators. The Institute, an independent not-for-profit organization based in Toronto and funded by the government of Ontario, will be a centre of excellence in cancer research, partnering with cancer research institutions across the province to achieve impact on cancer and economic benefits for the province.

Working with the Board of Directors and the Scientific Advisory Board, you will determine the strategic directions and research program priorities for the Institute. You will provide the scientific leadership for the organization; attract outstanding investigators and mentor promising young scientists; foster creative collaborations with institutional research partners and industry; and take a leadership role within the Ontario cancer research community.

Candidates should be internationally recognized as outstanding leaders in cancer research. This opportunity will take advantage of your proven ability to build a program as well as your experience with successful research collaborations. As a successful leader, you have demonstrated your capacity to build relationships and to work effectively with stakeholders.

If you are passionate about cancer, this is a unique opportunity to make a difference. For further information please e-mail **presidentsearch@oicr.on.ca**.

Interested candidates should send a detailed CV and personal history to: **Attention: Theresa Zember, OICR Search Committee, c/o Ontario Cancer Research Network, MaRS Heritage Building, Suite 335, 101 College Street, Toronto, Ontario, Canada M5G 1L7.** All inquiries will be treated in strictest confidence.

The Institute is an Equal Opportunity Employer.

A GREAT PLACE TO WORK

Chair of Bio Signals and Bio Systems

Department of Electrical and Electronic Engineering

This position will make significant contributions to the research activities of the Department, particularly in the area of signals and systems in the context of biology and/or biomedical engineering. Research leadership as exemplified by major research activities and PhD supervision is essential. The incumbent will undertake teaching in the broad curriculum offered by the Department and may be required to teach at both undergraduate and graduate levels. A commitment to excellence in teaching and an ability and willingness to teach a variety of undergraduate subjects is required. The incumbent will also perform administration commensurate with the position level.

Salary: An attractive remuneration package in accordance with expertise and experience is negotiable.
Employment Type: This is a full-time (continuing) position.
Enquiries Only To: Associate Professor Doreen Thomas, Head of Department, tel. +61 3 8344 6699, email d.thomas@ee.unimelb.edu.au
Applications: by 30 April 2006 quoting position no. G0004366
The Council reserves the right to make no appointment or to fill the Chair by invitation at any stage.

HOW TO APPLY

- For a position description and application details visit **www.unimelb.edu.au/jobs**
- Applicants must address the selection criteria in the position description, quote the relevant position number and include contact details of three referees.
- Applications to **hr-applications@unimelb.edu.au**

An Equal Opportunity Employer

EOWA EMPLOYER OF CHOICE FOR WOMEN

THE UNIVERSITY OF MELBOURNE

THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER

ASSISTANT/ASSOCIATE PROFESSORS: The Department of Physiology invites outstanding scientists with Ph.D., M.D., or equivalent degrees to apply for several faculty positions as tenure-track Assistant or Associate Professors. Candidates who use integrative and innovative molecular, genetic, biophysical, biochemical and systems biology approaches to analyze important biological problems are encouraged to apply. The scientific excellence of the candidates is more important than the specific area of research.

These positions are part of the continuing growth of the Department at one of the country's leading academic medical centers and will be supported by significant laboratory space, competitive salaries, and exceptional start-up packages. The UT Southwestern faculty, which includes four Nobel Prize laureates, 15 members of the National Academy of Sciences (NAS) and 17 members of the NAS Institute of Medicine, conducts more than 2,000 research projects that are supported by $300 million grant funding annually.

Applicants should submit curriculum vitae, a brief statement of research plans, and arrange to have three letters of reference sent to: **Helen L. Yin, Ph.D., Chair of Search Committee, c/o Gena McElyea, Department of Physiology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9040**.

UT Southwestern strongly encourages applications from women, minorities, and people with disabilities. An Affirmative Action/Equal Opportunity Employer.

WHO/TDR discovery efforts – Innovation with capacity building

Call for Applications

Seeking:

- **HTS against validated targets or appropriate model systems.** Investigators from industry and academia willing to run HTS campaigns, and those with validated or potential targets and assay development against TDR target disease parasites. Funding for fellows from developing countries on selected projects and training/mentorship.
- **Natural product-based lead discovery in developing countries.** Key requirements are availability of infrastructure for natural product R&D, *in vitro* or *in vivo* data from extracts or pure compounds, and established methods for identification/optimization of active agents including phytochemistry.
- **PK/metabolism centers for preliminary assessment of TDR lead compounds.** Institutions and PIs with relevant expertise to serve as PK/metabolism centers to progress leads coming out of TDR screens, and host fellows from disease endemic countries.

Application deadline: **17 February 2006**

Please visit the TDR website: **www.who.int/tdr** for more details and applications procedure.

For any questions, please contact Dr Solomon Nwaka (**nwakas@who.int**).

TDR

Assistant/Associate Professor
The Department of
Biochemistry and Molecular Biology

The Department of Biochemistry and Molecular Biology at the University of Louisville School of Medicine invites applications for a tenure-track Assistant/Associate Professor. The UofL School of Medicine has experienced a 200-fold growth rate in federal funding over the past 5 years and has built 2 new research buildings with ground breaking for a 3rd building set for this fall. Candidates must have a Ph.D. in Biochemistry or Molecular Biology or a related discipline. Individuals with an established, federally funded research program and whose expertise complements current strengths in environmental genetics, gene regulation, and cancer biology will be given preference. The successful applicant will benefit from a competitive start-up package, customized laboratory space, and numerous opportunities for collaborative interactions with multidisciplinary research centers focusing on environmental health, embryonic development, aging, cancer, cardiovascular disease, and stem cell biology. The individual recruited will be expected to teach in the Medical or Dental Biochemistry courses and to contribute to core and elective graduate courses.

Applicants should send a letter outlining research interests, curriculum vitae, and the names of at least three individuals who may be contacted for letters of reference to: **Assistant/Associate Professor Search Committee Department of Biochemistry and Molecular Biology, University of Louisville School of Medicine, Louisville, KY 40292**. Application review will begin **February 15, 2006** and continue until the position is filled. Applicants should be U.S. citizens, permanent residents, or currently hold an H1B1 visa.

The University of Louisville is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

PUBLISHERS (X3) AND EXECUTIVE EDITOR

We are: an international publisher of scientific journals and magazines, and a world leader in electronic publishing.

We seek: enthusiastic team players to join our busy Journals Publishing Department. In a highly visible role, you will be responsible for the editorial and financial success of several of our journals.

Publishers: we are recruiting for the following research areas:
medical physics; plasma physics; micromechanical engineering and smart materials (maternity cover only).

You will: combine a strong interest in all aspects of physics, and related areas, with excellent scientific judgement. You will have the energy and enthusiasm needed to establish and make the most of a network of scientific contacts to expand the content and impact of a number of our journals. You will work closely with authors, referees and Editorial Board members on papers submitted for publication at key stages of the peer-review process. Commercially aware, you will understand what it takes to make a profitable journal and have the interpersonal skills to take a proactive approach in developing the journal to be the first choice for authors and readers. Excellent communication and organizational skills are essential, as is a good understanding of the research physicist's expectations of a research journal. You will have at least a first degree in physics or a related subject and a minimum of two years' publishing experience.

Executive Editor – environmental science
In addition to the above skills and experience, you will be responsible for a dedicated website, and writing and commissioning summaries of key developments in the field. Ideally you will hold a PhD in environmental science and have work experience in research.

Starting salaries will be in the £22000–27000 range, depending on qualifications and experience.

Attractive benefits include generous holiday entitlement, pension, life assurance and medical insurance.

For an application form, which should be returned by 24 February, contact Lisa Palmer, Human Resources Assistant, Institute of Physics Publishing, Dirac House, Temple Back, Bristol BS1 6BE. E-mail: vacancies@iop.org. Tel: 0117 929 7481.

To apply for these roles, you must be legally entitled to work in the UK

Institute *of* **Physics** PUBLISHING **www.iop.org**

THE UNIVERSITY OF HONG KONG
香 港 大 學

The University of Hong Kong is at the international forefront of higher learning and research, with more than 100 teaching departments and sub-divisions of studies, and more than 60 research institutes and centres. It has over 20,000 undergraduate and postgraduate students from 48 countries. English is the medium of instruction. The University is committed to international standards for excellence in scholarship and research.

Associate Professor / Assistant Professor in the School of Chinese Medicine

(Ref.: RF-2005/2006-329)

Applications are invited for appointments as Associate Professor / Assistant Professor (various posts) in the School of Chinese Medicine, tenable from September 1, 2006. The appointments will initially be made on a two- or three-year fixed-term basis, with the possibility of renewal, subject to mutual agreement.

Applicants should have a Bachelor's degree in Chinese Medicine or Pharmacy in Chinese Medicine awarded by a tertiary institution in Chinese Medicine and a pertinent Ph.D. degree as recognized by the University. They should have at least 10 years of teaching, research and clinical experience, with a proven track record of publications in high-impact journals; and have successfully secured different types of research grants. Applicants should also have a good background for activating research in Chinese Medicine and Pharmacy in Chinese Medicine with modern science application techniques. Ability to speak fluent Cantonese or Putonghua is mandatory, while preference will be given to those who speak fluent English. The appointees are expected to undertake teaching, research and administrative duties and any other duties as assigned by the Director of the School. Further information about the School can be obtained at http://www.hku.hk/chinmed/.

Applicants should submit a completed application form, together with a curriculum vitae setting out their research experience, publications, research proposals, and other relevant details.

Starting annual salaries for **Associate Professorship** and **Assistant Professorship** are around HK$593,100 and HK$451,980 respectively (approx. US$1=HK$7.8) (subject to review from time to time at the entire discretion of the University). The appointments will attract a contract-end gratuity and University contribution to a retirement benefits scheme, totalling up to 15% of basic salary.

At current rates, salaries tax does not exceed 16% of gross income. The appointments carry leave, and medical/dental benefits. Housing benefits will be provided as applicable.

Further particulars and application forms (272/302 amended) can be obtained at https://extranet.hku.hk/apptunit/; or from the Appointments Unit (Senior), Human Resource Section, Registry, The University of Hong Kong, Hong Kong (fax (852) 2540 6735 or 2559 2058; **e-mail**: apptunit@hkucc.hku.hk). **Closes February 20, 2006**.

The University is an equal opportunity employer and is committed to a No-Smoking Policy

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US Environmental Protection Agency
Office of Research and Development
National Risk Management Research Laboratory

Associate Director for Ecology and Associate Director for Science

The U.S. Environmental Protection Agency (EPA) is seeking two proven scientific leaders for the positions of Associate Director of Ecology and Associate Director for Science in the National Risk Management Research Laboratory (NRMRL), Office of Research and Development (ORD), Cincinnati, Ohio. The Associate Directors participate with the Director of NRMRL in the planning, implementation and management of research development and demonstration programs assigned to NRMRL. The Directors provide leadership, direction and guidance to a multi-disciplinary staff and play a vital role in shaping the direction and outcomes of their respective area of research.

NRMRL's mission is to provide authoritative leadership in developing risk management research to provide a basis in support of policies, programs and regulations of the Environmental Protection Agency with respect to sustainable development, pollution prevention and control in industrial practices, prevention of release of toxic substances, safe drinking water, air pollution prevention, protection of water resources, ecosystems protection and land revitalization.

To learn more about NRMRL, please visit the website at:
http://www.epa.gov/ORD/NRMRL/

To learn about the positions, salary and qualifications, call or write to: **USEPA/OARM/OHR/SES Human Resources Staff (3650A), 1200 Pennsylvania Avenue, N.W., Washington, DC 20460** or visit **www.usajobs.opm.gov**. The vacancy numbers are: **EPA-06-SL-ORD-6369 (Eco)** and **EPA-06-SL-ORD-6370 (Science)**. Candidates must respond to the technical qualification requirements to be considered for the position. **U.S. Citizenship Required.** Applications must be received by the closing date of **April 21, 2006**.

EPA is an Equal Opportunity Employer.

NEUROSCIENCE FACULTY POSITIONS

We are seeking an outstanding individual to join an interdisciplinary group of investigators to study synaptic mechanisms of learning and memory. This is a tenure track appointment at the Associate or Full Professor level depending on experience. A variety of approaches from behavioral to molecular are welcome. This recruitment is part of the development of the new Synapses and Cognitive Neuroscience Center at the Medical College of Georgia (MCG).

Outstanding facilities are available for electron microscopy, multiphoton and other imaging, microarray technology, proteomics, transgenic animals, and clinical collaborations.

Candidates should have the Ph.D. or M.D. degree and a demonstrated capacity to perform creative, original, and funded research. The successful applicant will become a member of the Center with joint appointments in a clinical or basic science department. We offer a generous start-up package and outstanding facilities in a growing academic medical center.

The MCG is located in a historic city of 300,000 people with excellent recreational and lifestyle opportunities. Please send a letter of interest, curriculum vitae and names and contact information for 5 references to:

Kristen M. Harris, PhD
Medical College of Georgia
Synapses & Cognitive Neuroscience Center
1120 15th Street, CB-3731
Augusta, GA 30912
kharris@mail.mcg.edu

For more information see **www.mcg.edu** and **http://synapses.mcg.edu**.

MCG is an EEO/AA/Equal Access Employer and we invite applications from women and members of underrepresented racial minorities, and the handicapped (AC # 48504).

McGinty Endowed Chair in Marine Biology

FAU FLORIDA ATLANTIC UNIVERSITY

The Department of Biological Sciences at Florida Atlantic University (FAU) invites nominations and applications for the John Thomas Ladue McGinty Eminent Scholar chair position in Marine Biology. Candidates should be internationally recognized as distinguished leaders in their specific field of marine biology and currently have a well-established research program. We seek an individual deeply committed to both research and teaching, particularly at the graduate level, in order to enhance a new Ph.D. program in Integrative Biology. Special consideration will be given to candidates whose research takes full advantage of FAU's geographic proximity to the marine and estuarine environments of Florida and the tropical Atlantic-Caribbean region. Applicants from a diversity of subdisciplines will be considered including, but not limited to ecology, physiology, molecular biology and organismal biology.

The McGinty Eminent Scholar will conduct a program of research that facilitates collaborations with departmental faculty and strengthens current collaborations with Harbor Branch Oceanographic Institution (HBOI) and other marine institutes in the region. Biology faculty are actively involved in marine biological research at both the Boca Raton (www.science.fau.edu/biology) and HBOI campuses (**www.hboi.edu**). The Eminent Scholar will be active on both campuses having primary research space in the new 40,000 sq. ft. FAU-HBOI facility. He/she will be expected to guide the recruitment of several new junior faculty positions aimed at enhancing the Marine Biology initiative at FAU. The endowed chair position will be filled at the full professor level with a joint appointment at the Senior Scientist level at HBOI. Review of applications will start March 1, 2006 and continue until the position is filled.

Further information regarding the position can be obtained from **Dr. Rod Murphey (rmurph16@fau.edu)**,Chairman, Department of Biological Sciences. Applications and nominations should include curriculum vitae, five representative publications, a short description of research and teaching interests, and names and contact information of three referees. Submit applications electronically to: **Mrs. Lynn Sargent (lsargent@fau.edu) McGinty Eminent Scholar Search Committee, Department of Biological Sciences, Florida Atlantic University, 777 Glades Rd., Boca Raton, FL 33431.**

FAU is an Equal Opportunity/Equal Access Institution.

EMORY UNIVERSITY SCHOOL OF MEDICINE

TENURE TRACK POSITION

DEPARTMENT OF PHARMACOLOGY

A faculty position at **Assistant or Associate Professor** rank is available for an energetic individual taking a molecular, cellular and/or pharmacogenomics approach to cancer-related biomedical research problems. Candidates should have strong evidence of sustained creativity and a temperament that facilitates collegial and collaborative interactions in a matrix-organized cancer institute. Qualified Ph.D. or M.D. candidates with research interests in the areas of cell growth control, genetic instability, DNA repair, cancer biology, chemical biology, or anticancer drug discovery, and with a track record of research funding, are especially encouraged to apply.

Successful candidates will receive excellent new laboratory space in the Winship Cancer Institute (WCI) and competitive salary and startup funds in a setting that fosters their professional development. Our multi-departmental, division-based graduate programs provide a large pool of highly talented graduate students, and successful candidates will also participate in medical student training as well as the scientific programs of the WCI. Emory University is located in a wooded, residential area in suburban Atlanta, and has undergone rapid growth in molecular and cellular biomedical research programs including cancer research programs. Check us out at http://www.pharm.emory.edu.

Applicants should send curriculum vitae, representative reprints, a summary of current research and future plans, and names of three or more referees to: **Raymond Dingledine, Chairman, Department of Pharmacology, Emory University School of Medicine, Atlanta, GA 30322.** Please reference job vacancy **#204203**.

Emory University is an equal opportunity/affirmative action employer and encourages the application and nomination of qualified minority and female candidates.

BCM Baylor College of Medicine

NHLBI Training Center In Molecular Cardiology

Our NIH-funded postdoctoral training program in Molecular Cardiology, directed by Drs. Michael Schneider and Doug Mann, is available to outstanding MDs and PhDs alike. Areas of particular excellence include cell and gene therapy for cardiovascular disease, human genetics, myocardial ischemia and inflammation, atherosclerosis and lipoprotein research, cardiac development, and heart failure.

More than two dozen distinguished mentors are available. Our research is supported principally by the NIH, including large multi-investigator NHLBI Program Project Grants in cardiovascular gene therapy, genetics of congenital heart disease, myocardial ischemia, and cardiovascular development. Work on cell therapy for cardiac repair is supported by an NHLBI Specialized Center for Cell-Based Therapy for Heart, Lung, and Blood Diseases, and by a Transatlantic Network of Excellence for Cardiovascular Research from the Fondation Leducq.

Molecular Cardiology research is housed by Baylor College of Medicine's main campus, our adjacent clinical facilities (Texas Heart Institute, St. Luke's Episcopal Hospital, Texas Children's Hospital, The Baylor Clinic, Ben Taub General Hospital, Michael E. DeBakey Veterans Affairs Medical Center) and other contiguous participating institutions. The 170,000 sq. ft. Margaret M. Alkek Building for Biomedical Research, to be completed in late 2006, will house expanded space for cardiovascular research, diabetes, metabolism, and enabling technologies.

Physician-scientists seeking a combined fellowship in Clinical Cardiology (24 months) plus Molecular Cardiology research (24-36 months) should contact the Section of Cardiology directly: **Sonia Fuentes, Fellowship Coordinator, sfuentes@bcm.tmc.edu**. All other candidates for post-doctoral research in Molecular Cardiology (PhDs, or physicians taking a training sequence alternative to the above) should send their inquiries to **Michael D. Schneider, MD, Program Director, michaels@bcm.tmc.edu**.

Candidates must be citizens or non-citizen nationals of the US, or have been lawfully admitted for permanent residence. Baylor College of Medicine is an Equal Opportunity/Affirmative Action/Equal Access Employer.

Careers at La Trobe

www.latrobe.edu.au/jobs/

Lecturer/Senior Lecturer in Chemistry

Applicants with a background in medical chemistry and biological chemistry are encouraged to apply.

Full-time, continuing (Level B/C) position in the School of Molecular Sciences, Department of Chemistry

Remuneration package for Level B is $71,285 to $84,651 per annum, and Level C is $87,322 to $100,689 per annum (Level C), which includes 17% employer superannuation.

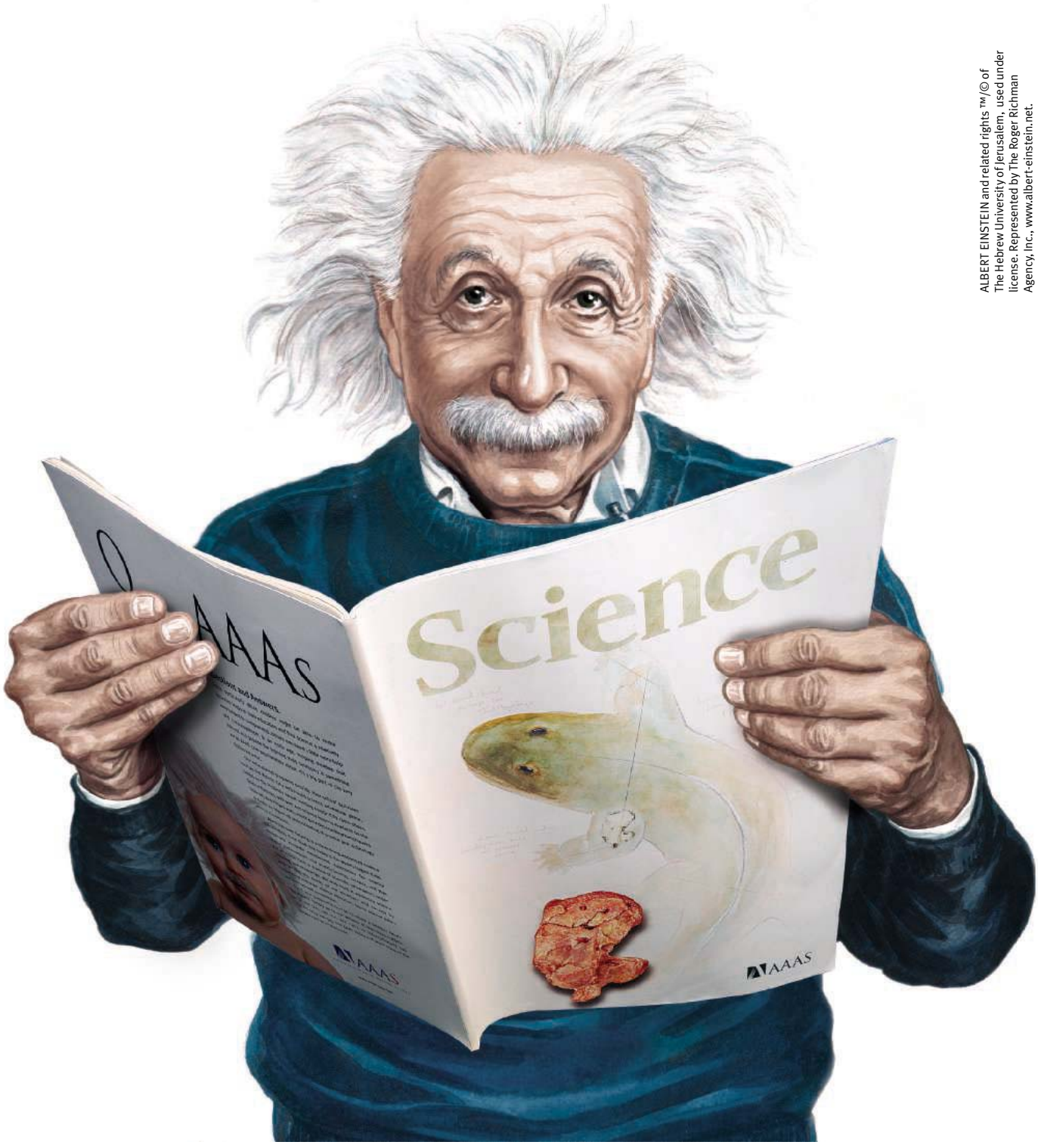
Reference no: 50015432
Campus: Bundoora
Closing date: Close of Business, Friday, 3 March 2006

Applicants must obtain details of how to apply by visiting our website, email – jobs@latrobe.edu.au or telephone (03) 9479 1365, quoting appropriate position numbers. La Trobe University is an Equal Opportunity Employer.

LA TROBE UNIVERSITY

LAT0239

La Trobe. The right choice for you.



Albert Einstein

1879–1955

POSITIONS OPEN

RESEARCH ASSOCIATE
Molecular/Cellular Biology and MRI

A Research Associate position is available for a Cellular/Molecular Biologist in the Department of Biological Sciences at Carnegie Mellon University. Candidates will participate in the development of novel agents for in vivo cellular/molecular imaging utilizing magnetic resonance imaging (MRI). Previous experience with MRI is nonessential. A Ph.D. is required, with a background in a broad range of recombinant DNA techniques; construction of viral vectors and/or transgenic technologies; gene expression detection methods; mammalian tissue culture; strong scientific problem solving skills; ability to communicate results in a clear manner verbally and in writing; record of scientific achievement as documented by peer-reviewed journal publications.

Interested candidates should send curriculum vitae and names of three references to: **Dr. Eric T. Ahrens, Department of Biological Sciences, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, PA 15213 U.S.A. Fax: 412-268-7083; e-mail: eta@andrew.cmu.edu.** *Carnegie Mellon is an Equal Opportunity/Affirmative Action Employer.*

NIBR PRESIDENTIAL POSTDOCTORAL FELLOW

The Presidential Postdoctoral Fellow Program of the Novartis Institutes for BioMedical Research (NIBR) provides talented Scientists with a unique opportunity to perform high quality science at one of our global sites in Basel, Switzerland; Cambridge, United States; Horsham, United Kingdon; or Vienna, Austria. Each year, innovative scientists from academia are selected to become Fellows and collaborate with leading pharmaceutical discovery Scientists pursuing multidisciplinary research projects. Fellows are appointed to a single three-year term to work on the proposed research they would conduct at NIBR. Graduate students within six months of completing their doctoral work and postdoctoral fellows nearing completion of their first postdoctoral training period (within three years of obtaining their Ph.D.) are eligible to apply. Fellows are competitively selected after three rounds of interviews and the review of a written project proposal. Application instructions can be found on our **website: http://www.nibr.novartis.com/Careers/Postdoc_fellowships/index.shtml.**

FACULTY POSITIONS

The Department of Cell Biology and Physiology of the University of Pittsburgh School of Medicine invites applications for Tenure-Track Positions at all professorial levels. Departmental research strengths include: epithelial cell biology and transport, regulation of membrane traffic, signaling in reproductive, endocrine, and cardiovascular systems. We seek individuals whose research will interface with and extend the existing strengths of the Department and those of the broader institution. Space and startup funding is generous and competitive with other top ten research institutions.

Applicants should have a Ph.D. and/or M.D. degree and postdoctoral experience. Send curriculum vitae, summary of research interests, and names of three references to**: Raymond A. Frizzell, Ph.D., Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, S367 Biomedical Science Tower, 3500 Terrace Street, Pittsburgh, PA 15261.** *The University of Pittsburgh is an Equal Opportunity/Affirmative Action Employer.*

ASSISTANT PROFESSOR, FOODS AND HEALTH. The Department of Food Science and Nutrition, University of Minnesota, nine-month, tenure-track position. See **website: http://fscn.che.umn.edu/** for details. *The University of Minnesota is an Equal Opportunity Educator and Employer.*

POSITIONS OPEN

FACULTY POSITION IN BIOCHEMISTRY
University of Dayton

The University of Dayton (UD) Department of Chemistry invites applications for a full-time, nontenure-track position in biochemistry, effective August 16, 2006. This appointment at the Visiting Assistant Professor level may be renewed for additional years. A Ph.D. in biochemistry is required at the time of the appointment and postdoctoral experience is desirable. Candidates with strong potential for excellence in teaching undergraduate and graduate students who will complement Department research efforts in biochemistry and medicinal chemistry are sought. Primary teaching responsibilities include both lecture (a two-semester biochemistry sequence and a one-semester biochemistry course) and biochemistry laboratory. Opportunities may exist to teach other advanced or lower level chemistry courses. Collaborative research with undergraduates is expected and institutional support for mentoring research projects will be provided. Summer support, which may include teaching a biochemistry course, is also available. The Department of Chemistry has nine full-time faculty positions and offers B.A., B.S. (American Chemical Society certified) and M.S. degrees. UD is Ohio's largest private university and one of the top ten Catholic universities. The Research Institute, one of the nation's largest nonmedical research institutes, provides basic and applied research for industry and government, including the Air Force Research Laboratory at Wright-Patterson Air Force Base. To apply, submit electronically a cover letter addressing professional background and goals, a statement of teaching philosophy; a research summary; a curriculum vitae; undergraduate/graduate transcripts; and names and contact information of three professional references to**: Dr. Albert V. Fratini, Chair of Biochemistry Search Committee** at **e-mail: albert.fratini@notes.udayton.edu.** Review of applications will begin on March 1, 2006, and continue until the position is filled. For more information about the Department and the position, visit **website: http://www.udayton.edu/~chem/biochemsearch.** *The University of Dayton, a comprehensive Catholic university founded by the Society of Mary (Marianists) in 1850, is an Equal Opportunity/Affirmative Action Employer. Women, minorities, individuals with disabilities, and veterans are strongly encouraged to apply. The University of Dayton is firmly committed to the principle of diversity.*

FACULTY POSITION
Tufts University
Cummings School of Veterinary Medicine

Assistant/Associate Professor. The Department of Biomedical Sciences at Tufts Cummings School of Veterinary Medicine is seeking applicants for an Assistant/Associate Professor position in the area of reproductive biology and/or neuroscience with expertise in molecular endocrinology and/or gene regulation. The Section of Reproductive Biology within the Department presently maintains active research programs in neuroendocrinology, behavioral neuroscience, and biotechnology. The candidate should have a Ph.D. and/or D.V.M. plus two to three years of postdoctoral training. The successful candidate is expected to conduct independent and extramurally funded research and participate in our veterinary physiology or developmental biology courses and in the graduate programs. Evidence of a funding history and a record of teaching excellence are preferred and are required for the Associate Professor position. Interested candidates should submit a letter of application and curriculum vitae, along with a statement of career goals, and the names of three references to: **Dr. Arthur Donohue-Rolfe, Acting Chair, Department of Biomedical Sciences, Tufts University, Cummings School of Veterinary Medicine, 200 Westboro Road, North Grafton, MA 01536.** The Grafton campus is located 35 miles west of Boston. Applicant evaluations will be reviewed upon receipt until a qualified candidate is hired. *Tufts University is an Equal Opportunity/Affirmative Action Employer.*

UNIVERSITY of CALIFORNIA
Riverside

FACULTY POSITION IN COSMOLOGY/PARTICLE ASTROPHYSICS
Department of Physics

The Department of Physics at the University of California, Riverside, is seeking an outstanding individual for a faculty appointment in the area of cosmology/particle astrophysics. This appointment will initiate a new program at UCR, which will complement existing programs in Astronomy, Astrophysics and Elementary Particle Physics. The appointment will be at the Assistant, Associate or Full Professor rank, as appropriate. The appointment will be effective July 1, 2006.

We encourage applications from candidates capable of instituting and sustaining a vigorous research program, and having an outstanding record of research achievement and leadership in one or more areas relevant to the field, such as dark matter or dark energy, structure formation, or the early universe. Candidates are also expected to support the training of graduate students and teach at the undergraduate and graduate levels. Salary will be competitive and commensurate with qualifications and level of appointment.

Applicants should submit curriculum vitae, list of publications, statement of research and teaching objectives, and names and addresses of four references. Applications should be directed to: **Chair, Cosmology Search Committee, Department of Physics, University of California, Riverside, 3401 Watkins Drive, Riverside, CA 92521-0413**

Review of applications will commence on **February 1, 2006**, but the position will remain open until filled. For more information please visit the UCR web site at **www.ucr.edu**, the College of Natural and Agricultural Sciences at **www.cnas.ucr.edu**, and the Department of Physics at **http://www.physics.ucr.edu/** .

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Website: http://www.skcc.org/SKCC_conf_2006.html
Email: skcc@pcmisandiego.com

POSITIONS OPEN

The Department of Psychiatry at the **University of Pennsylvania's School of Medicine** seeks candidates for an **ASSISTANT OR ASSOCIATE PROFESSOR** position in either the tenure-track or the nontenure Clinician-Educator track. Track and rank will be commensurate with experience. The successful applicant will have experience in the field of neuropsychiatry with a focus on behavioral neuroscience, functional magnetic resonance imaging (fMRI). Applicants must have a Ph.D. or M.D. degree and have demonstrated excellent qualifications in education and research. Candidates should have research experience in application of fMRI or electrophysiology in human studies, preferably in area of memory and executive function. Individuals with training in developmental neuropsychology are encouraged to apply. Responsibilities include participation in multidisciplinary team of basic and clinical neuroscientists with opportunities to contribute to study of schizophrenia and other brain disorders while pursuing independent research. Opportunities for clinical and teaching activities are available. Please submit curriculum vitae and a letter of interest, along with three reference names to: **Dwight L. Evans, M.D., Professor and Chair; Raquel E. Gur, M.D., Ph.D.; REF #75, c/o A. Plotnick, Department of Psychiatry, University of Pennsylvania School of Medicine, 305 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021.**

The University of Pennsylvania is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.

Denison University, a selective liberal arts college, invites applications for three one-year positions (two **MOLECULAR BIOLOGISTS,** one **ORGANISMAL BIOLOGIST**) to begin in August 2006. The teaching load for each position is two courses with companion laboratories each semester; all courses have enrollments of 24 or less. Teaching responsibilities for each position are a sophomore-level course (cell and molecular biology or ecology and evolution, respectively), an advanced level course in the candidate's area of specialty (immunology desired for one of the Molecular Biologist positions), and a nonmajors course in biology. Demonstrated ability in undergraduate teaching is expected.

Ph.D. preferred. For a detailed description of the Biology Department and our curriculum, see **website: http://www.denison.edu/biology/.** Candidates should send letter of application clearly indicating the position and course preferences, curriculum vitae, statement of teaching philosophy, transcripts (graduate and undergraduate), and three letters of reference to:

Chair, Search Committee
Biology Department
Denison University
Granville, OH 43023

Review of applications will begin February 27, 2006, and continue until the positions are filled. Denison is an Affirmative Action/Equal Opportunity Employer. Women and minorities are encouraged to apply.

POSTDOCTORAL POSITION
Experimental Biophysics

Applications for a research position in experimental biophysics to begin in the spring-summer 2006. The successful candidate would join an existing research program that is studying the binding and conformation of single molecules, including phase and conformation changes in DNA. The position includes a close collaboration with theorists. The initial appointment would be for two years, with the possibility of renewal for a third year. Candidates should send curriculum vitae, publication list, and a description of recent research along with the names of three references to: **Mara Prentiss, Ph.D., Physics Department, Harvard University, Cambridge, MA 02138,** or e-mail to: **Jan Ragusa (e-mail: ragusa@physics.harvard.edu).**

Harvard is an Equal Opportunity/Affirmative Action Employer. We encourage applications from qualified women and/or minority-group members.

POSITIONS OPEN

DIRECTOR, Division of Elementary, Secondary, and Informal Education
DIRECTOR, Division of Research, Evaluation, and Communication
National Science Foundation,
Arlington, Virginia

National Science Foundation's (NSF) Directorate for Education and Human Resources (EHR) seeks candidates for two positions: Director, Division of Elementary, Secondary, and Informal Education (ESIE), and Director, Division of Research, Evaluation, and Communication (REC).

The Division of Elementary, Secondary, and Informal Education (ESIE) supports NSF's mission to advance the knowledge and practice of informal science education and to provide leadership and promote the development of the infrastructure and resources needed to improve pre-K through grade 12 science, technology, engineering, and mathematics (STEM) education throughout the United States.

The Division of Research, Evaluation, and Communication (REC) contributes to the broad field of educational research and improvement by funding projects through grants, contracts, and cooperative agreements.

Additional information about the Directorate's activities and activities in the Division of Elementary, Secondary, and Informal Education (ESIE) and the Division of Research, Evaluation, and Communication (REC) may be found at **website: http://www.nsf.gov/ehr/about.jsp.**

Appointment to either of these two Senior Executive Service positions may be on a career basis, on a one-to-three year limited term basis, or by assignment under the Intergovernmental Personnel Act (IPA) assignment provisions.

Announcements S20060040 and S20060041, with position requirements and application procedures, are posted on NSF's Home Page at **website: http://www.nsf.gov/about/career_opps/.** Applicants may also obtain the announcements by contacting: **Executive Personnel Staff, telephone: 703-292-8755** (Hearing impaired individuals may call **TDD 703-292-8044**). Applications must be received by February 17, 2006. *NSF is an Equal Opportunity Employer.*

DIRECTOR
Affymetrix Genomics Facility
University of North Texas Health Science Center

A state-supported, tenure-tract **ASSISTANT PROFESSOR** faculty position is currently available to direct the Affymetrix Genomics Facility at the University of North Texas Health Science Center. The successful candidate will also be expected to have or develop an independent, externally funded research program, advise graduate students, and teach in Department graduate programs including forensic genetics. Candidates must apply and submit their curriculum vitae through the Human Resources Service online applicant tracking system at **website: http://www.unthscjobs.com.** In addition, a summary of past research accomplishments, future research plans, current funding, a statement of teaching experience and/or interests, along with the addresses of three individuals for recommendations, should be mailed directly to:

Dr. Robert J. Wordinger
Professor and Chairman
Department of Cell Biology and Genetics
University of North Texas Health Science Center
3500 Camp Bowie Boulevard
Fort Worth, TX 76107
E-mail: rwording@hsc.unt.edu

Equal Employment Opportunity/Affirmative Action Institution

POSITIONS OPEN

SENIOR MEDICINAL CHEMIST, NIH MOLECULAR LIBRARIES, University of New Mexico. The College of Pharmacy, Department of Chemistry and the Cancer Research and Treatment Center at the University of New Mexico (UNM) jointly invite applications for a tenure-track Faculty Position in medicinal chemistry with a focus on drug discovery, at the **ASSOCIATE** or **FULL PROFESSOR** rank. The successful candidate will be expected to sustain an extramurally funded research program in conjunction with the New Mexico Molecular Libraries Screening Center. Applicants should have a strong background and research interest in drug discovery via design and synthesis of small molecules, and he/she will be expected to contribute to the leadership of the NIH Roadmap synthetic team. Experience in a college of pharmacy or training in pharmaceutical sciences is desired but not required. Successful candidates will also provide some instruction to professional pharmacy students in medicinal chemistry and to graduate students (M.S., Ph.D.) in the biomedical sciences and chemistry graduate programs. The primary academic affiliation for this position is the College of Pharmacy, however the successful candidate will also be expected to build strong multidisciplinary research collaborations between Pharmacy, Chemistry and the Cancer Research and Treatment Center. This position offers excellent opportunities for collaborative research, especially within the Molecular Libraries Screening Center Network, College of Pharmacy, UNM Department of Chemistry, UNM Cancer Center, EPR Center, School of Medicine, Lovelace Respiratory Research Institute and local national laboratories. Complete information regarding this position is available at the following **website: http://hsc.unm.edu/facultyjobs/singleposting.cfm?PID=429&ID=1 (Position # 5963).** Applications will be accepted until March 15, 2006, or until the position is filled. The position is available July 1, 2006. Applicants should forward curriculum vitae, signed letter of intent describing career goals, outline of future research plans, and the names and addresses of at least three references to:

Professor Larry Sklar, Chair; Senior Medicinal Chemistry Search Committee
c/o Linda Jurey
College of Pharmacy/MSC09 5360
1 University of New Mexico
Albuquerque, NM 87131-0001

The University of New Mexico is an Equal Opportunity and Affirmative Action Employer and Educator.

FUNGAL GENOMICS. The USDA, Agricultural Research Service, Crops Pathology and Genetics Research Unit located in Davis, California, is seeking a permanent, full-time scientist to conduct research on the causative agent of sudden oak death, *Phytophthora ramorum.* This is a 100 percent research position. The incumbent's responsibilities will include an examination of the biochemical and molecular mechanisms of pathogenesis exhibited by *P. ramorum.* Experimental approaches may include such topics as computational analysis of the *P. ramorum* genome for gene identification, assignment of putative gene function, comparative genomics, proteomics or an examination of global gene expression as a function of plant host infection and colonization. Microarray experience is highly desirable. Salary will be competitive and commensurate with experience. For details and application directions, see **website: http://www.afm.ars.usda.gov/divisions/hrd/index.html.** Announcement number ARS-X5W-0345. For additional information contact: **Dr. D. Kluepfel** at **telephone: 530-752-1137,** or **e-mail: dakluepfel@ucdavis.edu.** *U.S. citizenship is required.* Review of applications will begin March 10, 2006, and will continue until a suitable candidate is identified.

Additional job postings not featured in this issue can be viewed online at **website: http://www.sciencecareers.org.** New jobs are added daily!

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A joint call for proposals for both Descartes Prizes was published on 17 December 2005. The closing date for applications is 4 May 2006 at 17:00 (Brussels local time).

Guidelines, application forms and information are available on the Cordis website: http://fp6.cordis.europa.eu.int/index.cfm?fuseaction=UserSite.FP6DetailsCallPage&call_id=266

For further information, please visit the Descartes website: http://europa.eu.int/comm/research/descartes/index_en.htm
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Winner of the 2005 Descartes Research Prize

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Bill Bryson
Writer, United Kingdom
Winner of the 2005 Descartes Communication Prize

The Descartes Prize for Excellence in Scientific Collaborative Research

Since the launch of this Prize in 2000, 16 different projects have been rewarded, involving 105 teams from 24 EU and non EU countries, which achieved major scientific breakthroughs in key European research areas.

In 2006, €1.15 million will be shared among winners and finalists. Up to five winning teams will be rewarded a minimum of €200,000 each and five finalist teams will receive €30,000 each.

The Prize recognizes Europe's most outstanding scientific and technological results achieved through cross-border collaborative research.

Proposals for the Research Prize can be made directly by the research teams from appropriate public and private organisations. Universities and foundations may also submit candidate teams.

The Descartes Prize for Excellence in Science Communication

Now in its third year, this Prize intends to stimulate interest in science communication and to improve the quality of science communication towards the general public. It rewards creative achievements in the fields of television, radio, publishing, public events, etc.

Since 2004, 10 European personalities have won this prize, selected by a panel of leading EU scientists and media professionals. This year, up to five winners will receive a minimum of €50,000 each and five finalists €5,000 each.

This prestigious competition targets organisations or individuals who have already been selected as winners by European and/or national organisations which carry out existing science communication prizes of any kind.

Submission of proposals shall be made by these prize-giving organisations.

EUROPEAN COMMISSION
Community research

POSITIONS OPEN

CMDITR MANAGING DIRECTOR

The NSF Science and Technology Center on Materials and Devices for Information Technology Research (CMDITR), **website: http://stc-mditr.org,** is a leader in photonic/electronic/ optoelectronic research and education. The Center comprises over 200 active participants from eight university partners and maintains numerous collaborations with government and industry researchers. Responsibilities of the Managing Director include development of programs, policies, budgets, and proposals, coordination of all Center communications including website, database, meetings, and reports, and liaison with sponsors, academic departments, and advisory boards. Qualifications: Ph.D. in a relevant scientific field preferred. Experience in academic research-related administration, and proven leadership, communication, and team building skills. The successful candidate will reside in Seattle at the University of Washington but work extensively with faculty, students, and staff at partner campuses (e.g. Georgia Tech., University of Arizona). To apply, please visit **website: http://www.washington.edu/jobs,** select Staff Jobs, and search for Req 19130. *The University of Washington is an Affirmative Action, Equal Opportunity Employer.*

MEDICAL WRITER

Physicians' Education Resource (PER) is seeking a Medical Writer/Editor to join its team. PER is a medical education company, located in Dallas, Texas, specializing in the field of oncology. Successful candidates will be responsible for writing manuscripts from original data, reporting highlights from cancer meetings, creating slide sets for pharmaceutical companies, and editing and rewriting author-submitted manuscripts. This full-time position requires a Ph.D. in a biomedical science. Send resume and salary requirements to: **Barb Schmaedeke, Human Resources Director, 3535 Worth Street #185, Dallas, TX 75246. E-mail: hr@perlp.com.**

POSITIONS OPEN

VCU

POSTDOCTORAL POSITION
Department of Biochemistry
Virginia Commonwealth University
School of Medicine

A Postdoctoral position is available in the laboratory of **Dr. Paul Dent,** Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia, United States. The project involves the use of novel therapeutic agents in cells to manipulate signal transduction pathways and cell survival. The applicant must have a strong work ethic and background in biochemistry and molecular biology, and be able to interact with individuals in the laboratory of **Dr. Steven Grant.** Experience in the culture of mammalian cells and in the assessment of cell death is required. Please contact **Dr. Dent** at **e-mail: pdent@hsc.vcu.edu** with curriculum vitae and the names and addresses of three references. *Virginia Commonwealth University is an Equal Opportunity Employer.*

STAFF SCIENTIST/SCIENTIFIC PROGRAMMER (G-016684). Work with biology laboratory and software development team to evaluate large datasets from mass spectrometry instrumentation. Requirements: Ph.D. in biochemistry or related biological science field; one year of graduate-level coursework in object-oriented programming using C++, including experience with Java; and two years of data analysis of large-scale quantitative proteomics by liquid chromatography/mass spectrometry (LC-MS) and LC-MS/MS mass spectrometry. Full-time; Seattle, Washington. Send resume to: **Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue N., J1-105, Seattle, WA 98109.**

POSITIONS OPEN

POSTDOCTORAL POSITIONS are available at the **University of Maryland, College Park** beginning March 1, 2006, to develop recombinant Newcastle disease virus as a vaccine vector for animal and human diseases. Excellent BSL-3 laboratory facilities available. A Ph.D. degree in virology/molecular biology is required. Forward curriculum vitae, and the names of three references to: **Dr. Siba K. Samal, Department of Veterinary Medicine, 8075 Greenmead Drive, College Park, MD 20742. E-mail: ssamal@umd.edu.**

COURSE

SHORT COURSE IN TRANSLATIONAL BIOMEDICAL RESEARCH

The University of North Carolina (UNC) at Chapel Hill offers a Certificate in Biomedical Translational Research at the end of a month-long NIH-funded training program, "Major Challenges of Clinical Medicine: An Overview for Basic Scientists," which provides a brief but in-depth experience with translational research for basic scientists at early stages of their careers that may then alter their subsequent career paths. The training faculty comprises a distinguished group of investigators with extensive experience in translational research and in research training. Eligible applicants are graduate students and postdoctoral fellows in the basic sciences, broadly defined. The first iteration of the program will run May 1, 2006 through May 26, 2006, and the second June 29, 2006, through July 28, 2006, in Chapel Hill, North Carolina. There is no cost to participate. Some housing and/or stipend support may be available.

See the program's **website: http://www.med.unc.edu/roadmap/initiatives.htm,** for more information, contact numbers, and an application. Applications from students outside UNC are due on March 15, 2006, for the May program and April 15, 2006, for the summer program.

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